Frequently Asked Questions:
Plasmapheresis and Systemic Scleroderma

Background

Recently, I have been getting a lot of questions from scleroderma patients about what they need to do and where they need to go to try plasmapheresis (also called therapeutic plasma exchange or TPE) treatments for their systemic scleroderma. This has been prompted by two events:

1. In October 2015, an abstract and poster was presented at the American Association for Blood Banking annual conference of a case report that documented that for one patient with anticientromere positive limited systemic scleroderma, just using TPE alone on a regular basis was able to reverse virtually all disease symptoms over a three-year period and keep the disease in full remission for 19 years. The abstract itself is published in the September 2015 issues of the research journal Transfusion. The news organization Scleroderma News did a feature article on this unusual case report: http://sclerodermanews.com/2015/12/03/scleroderma-patient-long-term-remission-tpe-treatment/ and you can then read a full version of the actual case report here: http://sclerodermainfo.org/pdf/Long-Term_Plasmapheresis_Case_Report.pdf. I am the lead author of this case report and my co-authors and I are currently in the middle of the process of getting the full case report published. I am also the patient.

2. I am very active in a dozen Facebook scleroderma-related support groups as well as Inspire, run by the US Scleroderma Foundation. I recently published an updated backstory that discusses my medical history as well as my transition from a scleroderma patient in 1990 to becoming a scleroderma website author and recently a published author of scleroderma research. Here is a link to that backstory: http://sclerodermainfo.org/pdf/Ed.pdf.

The inquiries that I have been getting are mostly from patients with anticientromere positive limited systemic scleroderma (what I have). There are many different specific questions and comments about using plasmapheresis to treat scleroderma that I will address a little later in this document, but first, I want to give you an idea of why it will be very difficult to convince your doctor to be willing to try plasmapheresis treatments as well as to get your insurance company to pay for them, at least through 2016.

In June 2014, the Scleroderma Foundation’s Medical Advisory Board, which includes a number of the world’s top scleroderma researchers, sent me this position statement on scleroderma-related blood hyperviscosity and plasmapheresis after they reviewed an early draft of my Scleroderma FAQ (http://sclerodermainfo.org/faq):

“The cause or causes of scleroderma are complex and much remains incompletely understood about this condition. Autoimmunity, blood vessel dysfunction, and excessive production of...
collagen are known to be important features of scleroderma. Both genetic and environmental factors play roles in the development of this disease.

There are some small and nondefinitive studies that have looked at whether the viscosity of blood is abnormal in scleroderma. Although some of these studies report elevated viscosity in the blood of SSc patients, it is not at all clear that this is clinically important. Plasmapheresis is a procedure where the plasma component of blood is removed and replaced with plasma from blood donors. It is used in the treatment of hyperviscosity syndromes which are associated with blood disorders and which are very different from scleroderma. Plasmapheresis is occasionally used in the treatment of some rheumatologic conditions as well. One small open label trial looking at whether plasmapheresis had utility in scleroderma was performed and published in 1991 and showed some improvement in Raynaud’s and digital ulceration with plasmapheresis. Because more definitive research has not been published yet, and because of the possible side effects of the procedure, plasmapheresis is not generally used.”

Contrast that statement with an excerpt for an abstract titled “Therapeutic Plasma Exchange for the Treatment of Systemic Scleroderma: A Comprehensive Review and Analysis” that was recently accepted for a poster presentation at the American Society for Apheresis annual meeting to be held in May 2016 in Palm Springs, CA:

**Method**
A comprehensive review of the research literature was conducted during November and December 2015. Additional articles were found by reviewing all of the references in the original article list. Articles written in other languages were included only if the abstracts were in English.

**Results**
We identified 39 relevant articles that met our search criteria, involving a total of 552 patients. Twelve of these were individual case studies; the rest ranged from small observational studies to prospective clinical trials with control groups. Because of the very diverse nature of the included studies and the greatly varying protocols, it is difficult to provide quantitative summary data. However, a number of very clear observations can be made upon careful review of these articles.

- TPE was very well tolerated by almost all patients. Adverse events were very rare and in almost all cases mild.
- In all studies, the majority of patients receiving TPE showed improvements in both symptoms and laboratory markers, whether in short-term treatment of crisis situations or from long-term administration of regular TPE.
- Many patients experienced significant improvement in Raynaud’s symptoms and initial healing of digital ulceration after just 3 to 4 weekly treatments.
- While the effects of even a few TPE treatments often lasted for a number of months, only continued long-term treatments resulted in stabilization of symptoms or in one recent case report, sustained remission over a 21-year period.
- Venous access problems occurred in a significant minority of patients receiving long-term TPE, leading to cessation of TPE treatments in some cases and switching to central venous access in other cases.

While this new paper is focused on the use of therapeutic plasma exchange for treating systemic scleroderma, it is worth noting that in doing the background research for the
paper, we found more than 25 research papers that discuss the topic of scleroderma-related blood hyperviscosity.

As you can see by reading these two excerpts, there is a major disconnect between the perceptions of scleroderma researchers and clinicians and the significant volume of research that has actually been published on the topic of interest – using plasmapheresis/TPE as a treatment for systemic scleroderma. Unfortunately, until scleroderma researchers and clinicians become aware of this actual research, getting clinicians to be willing to try plasmapheresis will be very challenging.

My primary mission for 2016 is to try to begin to close this knowledge gap.

Research Goals for 2016

Publications

The survey article on the use of TPE to treat systemic scleroderma (SSc) that was just accepted as an abstract for the American Society for Apheresis conference in May as a research poster will be subsequently published as a full paper in a research journal. This paper is actually part two in a three-part series of papers that I am the lead author on that are targeted for research journal publication in 2016.

- The first paper was the case report described above that documented that for one patient with anticentromere positive limited systemic scleroderma, just using TPE alone on a regular basis was able to reverse virtually all disease symptoms over a three-year period and keep the disease in full remission for 22 years. In addition to the Scleroderma News article on the case report, you can then read a long version of the actual case report here: http://sclerodermainfo.org/pdf/Long-Term_Plasmapheresis_Case_Report.pdf.

- The second paper is the comprehensive review of all research articles on the use of TPE to treat SSc since the late 1970s that was mentioned above. That is in only in abstract form now as we are in the process of writing the research paper and the poster for the research conference. My expectation is that it will be submitted for publication by late April and published later this year.

- The final paper in this three-part series is actually the key paper in this series. It has a working title of “Scleroderma Blood Rheology: Implications for Treatment and Research”. You can read an informal technical article on scleroderma-related hyperviscosity here that is the basis for this future paper: http://sclerodermainfo.org/pdf/Hyperviscosity-US.pdf. What is important about this final paper is that it documents the research behind a novel theory about the source of early vascular damage in scleroderma that if correct, may lead to completely new treatment approaches that potentially could turn scleroderma into a manageable disease like diabetes (insulin) and now HIV/AIDS (antiretrovirals).

All of my interest in TPE is based on a hypothesis that I came up with in early 1993 following a comprehensive review of all of the research literature on scleroderma development and treatments that was then available. If my hypothesis turns out to be correct (and an increasing number of researchers are beginning to believe that it may be), then therapeutic plasma exchange is just one treatment approach that may be an effective treatment for a subset of scleroderma patients and a partially effective treatment for the rest of the patients. It has the advantage that is very safe with almost no significant side
effects. But for a number of reasons outlined in the hyperviscosity paper, it may ultimately not be the best treatment. In fact, my current thought is that a treatment which starts with a limited course of TPE and is then followed by targeted drugs or drugs combined with periodic follow-on TPE treatments may be better/cheaper in the long run and more effective for a larger group of patients.

**Other Activities for 2016**

Every three years the American Society for Apheresis (I will be presenting the TPE survey poster at the ASFA conference in May 2016) Guidelines Committee publishes new evidence-based guidelines for the use of therapeutic plasma exchange to treat various diseases. The guidelines are used by Medicare and private insurance companies in the US to determine whether or not TPE treatments are covered for various disorders. There are four classification categories:

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<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
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<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
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<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
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<tr>
<td>IV</td>
<td>Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
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The 7th edition of the TPE Guidelines is being introduced at the May 2016 ASFA conference. I have sent the working committee all of the papers that we identified doing the background research for the forthcoming survey article. Currently, TPE for treating systemic scleroderma is classified as Category 3, basically indicating that the research is unclear on whether or not TPE is effective for scleroderma. In most cases, Category 3 diseases are not routinely covered by Medicare or insurance companies. It is important to note that the current 6th edition Guidelines groups all variants of systemic scleroderma into a single disease, meaning that TPE would need to be shown to be effective in all variants of scleroderma before it could be changed to a higher category designation. With the introduction of ICD 10 last year, systemic scleroderma is now divided into subcategories for diagnostic purposes: M34.0 for diffuse variants of scleroderma and M34.1 for limited variants. I have asked the guidelines committee to split systemic scleroderma into two distinct subcategories corresponding to the ICD 10 diagnostic codes. The advantage of this is that it may turn out that after appropriate clinical trials are conducted, TPE is more effective at treating patients with limited scleroderma than diffuse scleroderma. Splitting systemic scleroderma into two distinct sub-diseases would allow for TPE for treating limited scleroderma to receive a different category classification than TPE
for treating diffuse scleroderma if research determines this to be the case. Currently, even
if TPE was shown to be very effective for treating limited scleroderma, the category might
not change because TPE was not shown to be effective in all types of scleroderma.

Response to Comments and Questions

Here are some of the questions and comments that I have received over the past few
months:

- Why doesn’t my doctor know about this? Much of the research on using therapeutic
  plasma exchange (TPE) for treating scleroderma was done back in the 80s and 90s and
  hasn’t been studied a lot in the US since then, although it has been studied more overseas
  in recent years. Current research efforts with scleroderma are mostly focused on trying
different immunosuppressant drugs as well as some more recent efforts to interrupt the
fibrotic processes that lead to skin fibrosis and internal organ damage.

- Where is TPE done? Almost any medium or large hospital will do TPE on a regular
  basis, but almost always for other diseases or conditions. Any hospital that offers TPE to
  treat other conditions can perform TPE for treating scleroderma. While TPE is relatively
  straightforward to do, since venous access can be challenging in some patients, it is best to
  have TPE done in a setting where the staff is very experienced in doing TPE in order to
  minimize any potential problems during the procedure.

- Can you recommend a doctor who does this? Currently, no doctor that I am aware of
  is doing TPE for treating systemic scleroderma, mostly because they are not aware of the
  research to begin with. In fact, while scleroderma researchers are aware of the
  hyperviscosity aspect of scleroderma, few clinicians are aware of it. TPE is actually
  considered the “gold standard” treatment for hyperviscosity syndromes so educating
  clinicians about scleroderma-related blood hyperviscosity should advance the process (the
  third paper in the series).

- My doctor says it’s too expensive. According to some recent research studies, the
  actual cost of a typical TPE procedure in a hospital setting is about $1200 per treatment.
  That is also the Medicare reimbursement rate for TPE. To put this in perspective, at a
  frequency of 16 treatments per year, which was the frequency used in the very long term
  case study mentioned above, that is about $20,000 per year. While not inexpensive,
  modern biologic drugs like Humira and Enbrel, which are now commonly used to treat
  rheumatoid arthritis, are actually more expensive than this.

- Will my insurance pay for this? Medicare does cover TPE for treating scleroderma
  when it is life-threatening and other treatments aren’t working and many private insurers
  follow Medicare guidelines. Some are more restrictive. Since scleroderma is definitely life
  threatening and realistically no current treatments work very well, that is a strong
  argument that can be made in dealing with your insurance company. In the very long
  term case report described above, private insurance paid for the TPE treatments from 1993
  to 2012 and Medicare has continued to pay for the procedure without any issues being
  raised at all.

- If I am willing to pay for this myself, can I get it done somewhere without a
  doctor ordering it? In the US and most other countries, a procedure like TPE is only
  available in a hospital setting and would require a doctor to order it.
My doctor says that I need a central access port surgically installed to do this. It is the case that with very-long term TPE, a significant percentage of patients will eventually have problems with normal peripheral venous access. The patient in the case study has had more than 355 treatments to date, all using normal peripheral venous access. There are different types of central access ports that can be implanted that allow TPE to be done more easily. Some carry a risk of infections and others start with more involved surgery (fistula). There is a new type of port called a Vortex™ port that is anecdotal reports suggest may be safer than some other types of access ports. There are also reports in the research literature indicating that TPE can be done using arterial access, but there are very few places where this technique is currently being used.

Let’s assume for a minute that future research demonstrates that TPE is an effective treatment for a subset of scleroderma patients and that you are in that group. Systemic scleroderma is generally a steadily progressive, disabling, and disfiguring disease with increased mortality rates. If you are able to undergo TPE treatments using regular peripheral venous access, as the patient in the case report has been able to do, the decision to try TPE treatments may be a relatively easy choice (if insurance coverage is available). TPE is an outpatient procedure that takes a couple of hours, and after the IV needles are placed, the most common problem is probably boredom unless you can watch a TV show or movie during the procedure. (Actually, one of the common minor side effects of TPE treatments is a temporary reduction in blood pressure. Watching an action movie or something else that can keep blood pressure elevated can actually help to reduce this side effect.)

On the other hand, if you are one of the people that are unable to undergo TPE treatments using normal peripheral venous access, then there is a tradeoff decision that needs to be made. is it worth having a port installed that can make TPE treatments easy to do, knowing that there is a potential risk of infections? Putting this into perspective, when patients are put on heavy-duty immunosuppressive drugs such as mycophenolate mofetil (CellCept) or cyclophosphamide (Cytoxan) that are known to have major side effects and potential long-term risks, they are making a major tradeoff decision – potential short-term improvement in symptoms and quality of life versus potential long-term complications that can be severe or even life threatening.

My doctor says that TPE can be dangerous. A recent paper published in *Transfusion and Apheresis Science* (Cid et al. 2014) summarized the results of 2730 TPE treatments in 317 patients over an 11-year period. There were a total of 90 “adverse events”, all of which were mild and did not prevent the TPE procedure from being finished. TPE is considered a very safe procedure, well tolerated by almost all patients.

I have diffuse scleroderma – is TPE appropriate for me? Many of the patients that showed improvements after TPE treatments in the research studies included in the forthcoming survey paper were diagnosed with diffuse variants of scleroderma, often with positive Scl-70 antibodies. The patient in the case report has anticentromere positive limited scleroderma and the 16 times per year protocol has been sufficient to put the patient into remission and maintain this for more than 19 years. It is not clear whether or not this treatment frequency would be sufficient to fully control symptoms in patients with diffuse variants of systemic scleroderma, which is generally more “aggressive” than limited variants, although the research suggests that TPE treatments at this frequency will definitely be helpful. It is likely that initial clinical trials will be done on patients with limited scleroderma, since it is more likely that TPE treatments will be effective in less aggressive variants of scleroderma. If future clinical trials show that TPE is effective on patients with limited scleroderma, then follow-up studies on patients with diffuse
scleroderma would be an appropriate next step, probably focused on determining optimum treatment frequencies in these more severe cases.

- I have Mixed Connective Tissue Disorder (U1-RNP Antibody Positive) – is TPE appropriate for me? Out of the 39 research papers reviewed for the abstract for the May 2016 ASFA conference, 4 were case reports involving patients with MCTD. All patients showed benefit from TPE treatments.

**Approaching Your Doctor and Insurance Company About TPE Treatments**

Understanding that this will probably be easier to do after all three of the research papers are published, it is probably not a bad idea to start the process of educating your physician about TPE now if this is a treatment approach that you are interested in trying. Note that it will be much more likely for you to get support for trying TPE if you have anticentromere positive limited scleroderma and are relatively early in the disease process since this was the situation reported in the case report.

**Step 1 – Educate Yourself**

The first step is for you to educate yourself fully about this case report and the background research behind it. That way, if your doctor is open to talking you about it and starts to bring up very appropriate issues such as the possibility of needing at some point a central access port to be able to do this for the long term, you can have an educated discussion with your doctor about the tradeoffs of trying something like TPE versus more conventional approaches with immunosuppressive drugs. To do this, you need to review the links to the Scleroderma News story, the case report itself, and the background technical article. (Links to all three of these are included below in the potential email to your doctor.) You can also always email me directly with any questions before you approach your doctor.

**Step 2 – Educate your Doctor**

Here is one approach that you might want to consider. The reality is that most patient visits are too short to bring up something new like trying TPE treatments. Now that almost all physicians are on an electronic medical record system, these often include patient portals where you can view your lab results, upcoming appointments, etc. These systems typically include messaging features where you can email your doctor with non-critical questions and comments. If you have access to this type of system, consider starting with an email something like this:

Dr. xxx, I am a member of an online support forum for scleroderma patients where we often learn about new research on scleroderma treatments, including new investigational drug studies. Recently, the research news service Scleroderma News did a story about a case reported presented at a medical conference last October about a patient with limited scleroderma who has been treated with nothing but regular plasmapheresis treatments for more than 22 years with great success. Not only did it reverse virtually all of the patient’s symptoms, the patient has remained in remission for the past 19 years.

In the discussions about this case report, we got links to the Scleroderma News story itself (http://sclerodermanews.com/2015/12/03/scleroderma-patient-long-term-remission-tpe-treatment/), an unpublished full version of the case report itself (http://sclerodermainfo.org/pdf/Long-Term_Plasmapheresis_Case_Report.pdf), and a long
technical article that discusses the background research behind this case report (http://sclerodermainfo.org/pdf/Hyperviscosity-US.pdf).

Since I seem to be similar to the patient in the case report, could you please read the news story, case report, and background information so we can discuss whether or not this approach makes sense for me?

If your doctor responds to this email with a willingness to at least look at the case report and discussion of the background research behind the case report, that is a good indication that you have a doctor that is at least willing to look at this potential treatment and work with you to determine if it makes sense to consider in your individual situation.

**Step 3 – Getting Insurance Coverage**

So let’s assume that your doctor is open to considering TPE. Unless you are independently wealthy (or just won the lottery), you will need your insurance company to pay for TPE treatments. If you are old enough to be on Medicare, with your doctor’s support, you are likely to be covered. The patient described in the case report has been on Medicare for more than three years and when the first claims for TPE were submitted to Medicare instead of the private insurance company that had been covering the TPE treatments for 19 years, we expected that Medicare might initially reject the claim, at least without an appeal. Medicare guidelines for the use of TPE to treat scleroderma basically indicate that TPE is covered for life-threatening cases where conventional treatments are not working. The reality is that all cases of systemic scleroderma ARE life-threatening (especially diffuse cases) and conventional treatments really do not work according to the research. For whatever reason, Medicare covered the treatments without any questions or need to appeal.

This is actually very important if you have private insurance coverage. Some private insurance plans exactly follow Medicare guidelines. If your insurance company is one of these, it may take some discussions but if your doctor is a strong advocate for you, you should be able to get coverage because Medicare covers it.

Other insurance companies are more restrictive and getting coverage will be more challenging. You may be able to make the argument that since Medicare covers it, your insurance company should cover it as well. However, as this is an individual decision on the part of the insurance company, it may be a hard sell before the research studies that we are working on are published.

Another possible approach to getting insurance coverage is to have your blood viscosity tested. Research shows that most patients with scleroderma have elevated blood whole blood viscosity (actually from clumped red blood cells, which is not the most common reason for elevated blood viscosity). Almost all insurance companies indicate that they will cover TPE treatments for “hyperviscosity syndromes”. While scleroderma is not yet understood by most clinicians to be a hyperviscosity syndrome, getting a test result showing elevated blood viscosity should be a strong argument for getting insurance coverage to try TPE treatments.

What will ultimately be needed to get widespread insurance coverage of TPE for treating scleroderma will be at least one carefully designed clinical trial that demonstrates that it is an effective treatment. I am in the process of working with the largest company that makes equipment used to do TPE treatments and trying to convince them to fund such a clinical trial. This initial clinical trial will only include patients that have anticentromere positive relatively early stage (within 10 years of initial symptoms) limited scleroderma, as
this is the most likely group to respond fully to this treatment approach. However, best case, the process of getting a clinical trial funded, recruiting patients, performing the clinical trial, and getting results published will probably be a minimum of three years from now. What this means is that the only way that you are likely to get TPE treatments now is to have a doctor who reads the published research, believes that it makes sense for you, and is willing to “go to bat” for you with your insurance company.

**Step 4 – TPE Treatment Protocol**

If any patient is able to reach the point of trying TPE treatments, our goal is to try to make sure that all such trials are done in a consistent manner in order to be able to pool the results for future publication as a series of case reports. This means standardized pre and post-treatment testing of a few important lab measures such as blood viscosity and ESR, as well as standardized treatment protocol (frequency, etc.). Please contact me for additional information on the recommended protocols if you and your doctor are willing and able to try TPE treatments.

**Summary**

At the present time, for the vast majority of patients with systemic scleroderma, trying an unproven, experimental treatment approach like TPE is probably not an appropriate choice to consider. The bottom line is that at least for now it will be difficult, but not impossible, to convince your doctor and insurance company to try TPE treatments. Once the research papers mentioned earlier in this article are published, you may have a better chance of getting physician support, which is THE critical first step in this process. You will need a doctor who is willing to be educated and also be a strong advocate for you with your insurance companies. But even more important, **you** need to fully understand the implications of trying a very experimental treatment approach like this and to make sure that this is something that you want to do and are willing to follow through with for the long run. It is very important to understand that at the present time, ANY treatment approach used with scleroderma is going to need to be done for the long term since even in the best of cases, if you stop treatments, symptoms will return.

If you have any other questions on TPE or my current research and educational goals, you can always email me directly at eharris@sclerodermainfo.org.

Ed Harris, Director
Scleroderma Education Project

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