The Scleroderma Education Project is a 501c3 non-profit organization focused on systemic sclerosis education and research. You can find our website at SclerodermaInfo.org.

The topic of this presentation is a treatment for systemic sclerosis called therapeutic plasma exchange or TPE.

A little background on systemic sclerosis. This is a term used to describe a family of rare autoimmune diseases with the common factor being abnormal skin fibrosis and thickening in association with Raynaud's. While the degree of skin fibrosis varies depending on the specific disease variant, all forms of systemic sclerosis include dysregulation of the immune system and extensive microvascular injury leading to fibrotic damage to internal organ systems, including the lungs, gastrointestinal system, kidneys, and heart. Most patients are women and initial symptoms typically start after age 30.

Systemic sclerosis has the highest mortality rate of any autoimmune disease. There are currently no FDA approved treatments for this disease, so any drugs used to treat patients are being used "off-label". No standard treatments have been shown to significantly alter the natural course of the disease, although some medications can help with specific symptoms.

The basic idea behind TPE is really very simple: if there are molecules such as antibodies circulating in the blood that are directly or indirectly causing disease symptoms, reducing the level of these molecules should lead to symptom improvements. As will be discussed later, there may be other mechanisms of action how TPE affects patients with SSc.

This diagram shows how TPE is performed. Two IV needles are inserted, typically one in each arm.
Blood is withdrawn from one arm and pumped into a centrifuge that spins the blood, separating the red cells, white cells, and platelets from the plasma.

The extracted plasma is discarded. By the way, this is pretty close to the actual color of plasma.

The discarded plasma is then replaced by a replacement fluid such as sterilized albumin. The albumin is recombined with the separated cells and then returned to the body through the other arm.

A typical TPE treatment takes about 90 minutes after the IV needles are inserted. During a single treatment, about two-thirds of the plasma is replaced, significantly reducing the levels of any destructive molecules that might be circulating in the plasma.

This shows a typical example of a patient receiving TPE. The TPE system runs quietly in the background and the patient is usually resting comfortably during the procedure.

TPE is a commonly used treatment for a number of diseases. Most of these diseases are blood, neurological, or renal disorders. While TPE is not commonly used to treat systemic sclerosis in the US, it is more commonly used in Europe and other parts of the world. In Italy, for example, TPE is a common, government approved treatment for systemic sclerosis.

<table>
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<th>Conventional Uses of TPE</th>
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<tr>
<td>- TPE widely used since 1978 for treating a variety of diseases</td>
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<td>- Most common uses are for neurological, hematological, and renal diseases</td>
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<td>- Mainstream treatment for diseases such as: Guillain-Barré syndrome, myasthenia gravis, hyperlipidemia syndromes, and Goodpasture syndrome</td>
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I am the corresponding author of a recent study that reviews all of the published research on the use of TPE as a treatment for systemic sclerosis. This review is published in the June 2018 issue of the “Journal of Scleroderma and Related Disorders.” Since it is published Open Access, it can be freely downloaded by anyone directly from the publisher’s website.

The major focus of this presentation is an overview of the review paper, including topics such as safety and cost that will be of interest to anyone wanting to better understand this treatment option.

We used standard academic research tools to locate an initial set of papers that met our search criteria. Additional articles were found by reviewing all references in these papers. In order to be included in the study, the abstract had to be in English. We commissioned translations of several key articles that were not in English.

We were able to find a total of 46 published papers that met our search criteria. These included case reports through full-blown randomized controlled trials. Excluding patients in control groups, these studies involved a total of 455 patients treated with TPE.

Once we had a final set of articles, these were independently graded by two authors using standard checklists based on the article type.

Another key factor that we looked at was whether the patients were treated with TPE alone or if additional treatments such as immunosuppressants were co-administered, potentially confounding the interpretation of any results.

Twenty five of the 46 studies used TPE as the sole systemic treatment.
In almost all studies, the majority of patients receiving TPE showed improvements in both symptoms and laboratory markers, whether in short-term treatment for crisis situations or from long-term administration of regular TPE.

Many patients experienced significant improvement in Raynaud’s symptoms and if they had digital ulcers, these started to heal after just three to four weekly TPE treatments.

While the effects of even a few TPE treatments often lasted for several months, only continued long-term treatment resulted in stabilization of symptoms or, in one recent case report, sustained remission over a 22-year period.

Venous access problems occurred in a small number of patients receiving long-term TPE. TPE had to be stopped in six patients, and 12 patients ended up having TPE done through implanted central ports.

TPE was extremely well tolerated by virtually all patients. Adverse events were rare and, in almost all cases, mild, with no reported deaths.

One important question is whether TPE is equally effective for different variants of systemic sclerosis, for example, diffuse or limited. In many of the early studies, diagnosis was either not specified or pre-dated the 1980 classification criteria. However, where diagnosis was clearly indicated, most studies were done on patients with a diagnosis of diffuse systemic sclerosis.

Unfortunately, since treatment protocols varied widely in the reviewed studies, there is no way of comparing treatment outcomes to answer this question.

Mixed Connective Tissue Disease is a complex connective tissue disorder defined by overlapping clinical features of lupus, systemic sclerosis, and polymyositis. Six of the 19 case reports were about patients diagnosed with MCTD. In all six cases, TPE was initiated because of an acute or crisis situation rather than as a general treatment. Improvements were reported in all of these cases, although multiple simultaneous interventions in three of these cases make it difficult to determine the role of TPE in the observed improvements.

In a number of the studies, TPE was tried as a last resort after all other treatment approaches had failed. What is clear from these studies is that TPE is not an effective treatment for scleroderma renal crisis, now commonly treated with ACE inhibitors. It also had little or no benefit in patients with late stage diffuse systemic sclerosis where patients had severe lung damage.

The clear consensus was that TPE should be started relatively early in the disease process in order to have the maximum benefit.
All of this leads to an obvious question. Given that the published research suggests that TPE often leads to significant improvements in symptoms and laboratory markers even after a short series of treatments, what might happen if TPE was tried as a sole, systemic intervention over a long period of time? To date, there is only one published case report that helps to address this key question about the effects of long-term TPE, and fortunately, in this case, long-term is VERY long term!

It is, of course, important to realize that a single case report is suggestive at best, but with a disease like systemic sclerosis, which does not go into remission on its own, this case report is quite intriguing.

This male patient developed Raynaud’s symptoms beginning in 1985 at age 38. Initial ANA and antibody testing done in early 1990, combined with then current symptoms, lead to a formal diagnosis of CREST syndrome.

The patient’s symptoms progressed rapidly over the next several years. Of all of these clinical symptoms, the most concerning was the reduced lung function. The primary mortality risk with this variant of systemic sclerosis is from pulmonary artery hypertension, and a DLCO value under 70% can be a leading indicator for future development of this complication.

The protocol used in the case report was one treatment per week for four weeks followed by eight weeks of rest, repeated indefinitely. This was based on the research indicating that RBC aggregation levels were still significantly reduced after three months post-TPE, but rising. It is also important to note that there were no simultaneous systemic interventions such as immunosuppressants while the patient was on TPE.

Over a two year period that included a total of 32 TPE treatments, the patient’s symptoms steadily improved and by the end of year two, the patient was clinically in remission with the exception of very mild Raynaud’s. The patient’s GERD was completely under control and the chronic chilling symptom was completely gone as well. Lung functioning stabilized and slowly improved over the next few years and the last time a pulmonary function test was done back in 2001, the DLCO measure had risen to the low end of normal range.

The patient is still receiving regular TPE using the original protocol. At this point, the patient has received almost 400 TPE treatments. He is now 70, very active physically, and is in overall excellent health for his age. He is symptom free except for very mild Raynaud’s.

During 1997, treatments were stopped to observe the natural course of the disease. Reflux symptoms returned about six months later. The original protocol was reinstated and the reflux disappeared again after a year. Recent high magnification nailfold capillaroscopy demonstrated slightly abnormal capillaries that would be typical for early stage limited systemic sclerosis, in spite of the fact that the patient is 28 years post diagnosis. All of the observational data suggest that what this treatment protocol is doing is keeping the patient always one step away from redeveloping clinical symptoms.
A second patient has now been on the same pulsed TPE protocol described in the long-term case report for about 18 months. She has a rare (about 4%) antibody, U3-RNP (fibrillarin), that is mostly associated with diffuse skin changes. Her main complaints were severe pain and fatigue, both of which resolved after three treatment rounds. She is continuing with the same pulsed TPE protocol with a goal of retaining her current remission status.

When TPE was first tried in the late 1970s, the reasoning was that reducing levels of antibodies might help symptoms. However, antibody levels return to near pre-treatment levels within a few days after a TPE treatment.

Many early papers commented that they were surprised how long the effects of a few weekly TPE treatments lasted. In one 1991 study, improvements in both symptoms and laboratory markers persisted for six months or longer after a single round of four weekly TPE treatments.

So how do we explain the effects of TPE? One possibility is that the benefits are primarily stemming from improvements in blood rheology rather than temporary reduction of antibodies or other molecules.

Over the past 42 years, a number of studies have documented that systemic sclerosis patients have elevated whole blood viscosity and abnormal aggregation of red blood cells. This is not unique to systemic sclerosis; elevated blood viscosity and red blood cell aggregation are also seen in lupus and rheumatoid arthritis. Interestingly, TPE is not effective in these diseases.

Another interesting finding is that patients with primary Raynaud’s have normal blood viscosity and red blood cell aggregation. TPE has no effect on patients with primary Raynaud’s but significantly improves or completely eliminates Raynaud’s in many systemic sclerosis patients following a single round of TPE treatments.

Two recent studies have documented a correlation between elevated whole blood viscosity and both digital ulcers and pulmonary artery hypertension in SSc patients.

As early as 1979, researchers hypothesized that all of the symptoms seen in systemic sclerosis stem from repeated trauma to the endothelial layer of the microvascular system. One intriguing possibility is that this trauma is from clumped red blood cells. If this is the case, it is possible that the elimination of red blood cell clumps that follows a series of TPE treatments may be part of the process that leads to symptom improvements following TPE.
The smallest microcapillaries are slightly smaller than average red blood cell size, meaning that the red blood cells have to deform slightly for normal circulation.

Consider what might happen if there are small clumps of shear-resistant red blood cells. It is possible that small clumps might be forced through the microvascular system, at least for a while, but this could potentially lead to trauma to the endothelial cell layer. If the clumps are small, this damage might occur over a long period of time and might account for the fact that in slower progressing variants of systemic sclerosis, Raynaud's is typically the only symptom for a number of years.

In contrast, in diffuse systemic sclerosis, initial symptoms are often pain and fatigue. If the RBC clumps are large enough to impair blood flow in these faster progressing disease variants, this could potentially explain these initial symptoms.

Since the effects of a few weekly TPE treatments includes elimination of red blood cell clumping that lasts for more than three months before returning to baseline levels, this refractory period might allow for healing of damaged microcapillaries. This could lead to reduction of Raynaud's symptoms and healing of digital ulcers - a common finding in a number of studies.

In 1991, a carefully done study looked at how a series of four weekly TPE treatments modified overall blood viscosity and also red blood cell clumping. This diagram shows what happens to red blood cell clumping if you do a series of four weekly TPE treatments, then stop and watch what happens. The green horizontal line shows the level of red blood cell clumping in a control group of people without scleroderma. The red horizontal line shows the average amount of RBC clumping in the scleroderma group that received the four weekly TPE treatments.

As you can see, even after the first TPE treatment there is a noticeable drop in red blood cell clumping. After four weekly TPE treatments, the red blood cell clumping was completely gone and overall blood viscosity was normal as well. Now notice what happens once TPE is stopped: the viscosity immediately begins to increase again, but does so fairly slowly. Three months later, red blood cell aggregation levels are still only about half of what they were before TPE. At nine months post-TPE, red blood cell clumping was back to pre-TPE levels. Unfortunately, the researchers did not check red blood cell clumping levels between three
and nine months after TPE stopped, so we don’t know exactly at what point red blood cell clumping returned to baseline levels.

So now let’s look at what we believe happens if you use our suggested pulsed TPE (one TPE treatment per week for four weeks, wait eight weeks, repeat indefinitely). Eight weeks after the fourth TPE treatment, red blood cell clumping is beginning to return to pre-treatment levels, but is still quite low. As soon as you start the next TPE series, red blood cell clumping levels will immediate begin to fall and should be back to normal again after the fourth TPE treatment in this series, and the cycle starts again.

The goal of pulsed TPE is to interrupt the entire disease process at a very early stage before any significant fibrosis or organ damage has occurred. If there is already systemic involvement, the hope is that by preventing the ongoing trauma occurring to blood vessels, disease progression will be halted. With no new disease activity taking place the body may be able to heal to some extent unless organ systems are too severely damaged to recover.

The key and as of yet unanswered question is this: assuming that the overall disease model is correct, which needs to be determined by carefully designed research, what is the level of red blood cell clumping that the body can tolerate before systemic damage starts to occur? In other words, is there a “green zone” where pulsed TPE can prevent further damage and allow people to be mostly symptom free, even though they still have the underlying disease?

Pulsed TPE is designed to be a control, not a cure, similar to how insulin can interrupt diabetes or antiretroviral drugs can prevent HIV from progressing to AIDS, even though the underlying disease is still active.

Eleven of the reviewed studies documented complications directly related to the use of TPE. In almost all cases, these were either problems related to venous access or short-term side effects with the procedure itself. There were no reported fatalities and short-term side effects were generally minor.

Since TPE is a widely-used procedure for many diseases, there is a lot of data available on TPE safety. A recent large scale study of TPE indicated that adverse events occurred in only 3% of the procedures. A larger study of 20,000 procedures showed similar results. There were no fatalities reported in either study.
It is notable that almost all of the more severe complications were allergic reactions when fresh frozen plasma was used instead of sterilized albumin as the plasma replacement fluid.

Several studies have documented that patients undergoing long-term TPE often develop mild iron deficiency anemia. It is easily treatable using OTC iron supplements. If patients can't tolerate OTC iron, iron infusions can easily be done in conjunction with TPE treatments.

The best way to do TPE is using normal peripheral venous access, drawing blood from the antecubital vein. A number of studies have been done looking at how often normal venous access can be used for long-term TPE. Most of these studies indicate that about 75% of the time, normal venous access is fine for long-term TPE, but about 25% of the time, patients need alternative access such as surgically implanted ports.

Recently, however, new equipment and procedures have been developed that should significantly reduce the need for surgical ports. These include systems like VeinViewer and ultrasonic-guided peripheral venous cannulation.

For patients who cannot undergo normal peripheral venous access, there are a number of alternatives that are available. Central catheters are not a good option because of the significant risk of infection. Alternatives such as surgically created fistulas or implantable vascular-access ports may be better options for long-term TPE if peripheral venous access is not an option. Modern implanted venous access ports are much safer and effective than previous generations options.

The cost of TPE varies somewhat based on the amount of albumin that is needed for the individual patient. On average, a TPE treatment costs about $1200, according to recent research. Notably, this is almost exactly what Medicare pays for a typical single-blood volume exchange TPE treatment.

For comparison purposes, Humira is one of the least expensive biologic drugs used to treat rheumatoid arthritis. The typical annual cost for Humira is about $21,000. If TPE is used at a frequency of 16 times a year, that runs just under $20,000.

In contrast, another experimental treatment approach that is currently being tried for treating systemic sclerosis is IVIG. That costs, on average, about $10,000 a month for a typical 70-kg patient.
Currently, the American Society for Apheresis classifies TPE for treating systemic sclerosis as a Category III treatment, meaning that the efficacy is unclear and that clinicians should make individual decisions on whether to use TPE or not.

Medicare covers TPE for treating systemic sclerosis if: 1) the disease is life threatening, and 2) other treatments are not working. Considering that systemic sclerosis has the highest mortality rate of any autoimmune disease, and no conventional treatments have been shown to have any clear effect on the natural progression of the disease, this is a rather low bar for obtaining Medicare coverage.

A recent informal survey suggests that most companies in the US now cover TPE, sometimes with prior authorization needed.

To find out if your insurance company covers TPE, ask them if they cover CPT code 36514 for treating a diagnosis of M34.0 (diffuse) or M34.1 (limited), depending on your diagnosis.

While research suggests that it is common to see improvements in laboratory markers, Raynaud's symptoms, and initial healing of digital ulcers after one round of four weekly TPE treatments, this is not a clear indication that TPE is going to be effective in the long term. Remember, it took two years for the patient to go into nearly full remission in the case report I just described.

Our recommendation is that any trial of TPE should be continued for a one-year period. If there is no clear improvement at that point, it is very unlikely that TPE will be beneficial.

A good way to think about TPE as a treatment for systemic sclerosis is to consider the use of insulin for patients with diabetes or anti-retroviral drugs for patients with HIV. Systemic sclerosis is a lifelong, chronic disease and ANY treatment that does not fix the malfunctioning immune system will need to be continued indefinitely. This includes drugs commonly used to treat systemic sclerosis as well as TPE.

A typical TPE treatment takes about 1 1/2 hours. Once the IV needles are inserted, there is little pain or discomfort during the treatment, although there can be mild paresthesias or perioral tingling from the use of citrate as an anticoagulant. In addition, patients may experience mild hypotension. These symptoms can easily be prevented or are easily dealt with during the procedure if they occur. Immediately following a TPE treatment, it is common to feel a bit tired for 12 to 24 hours.

Any MD (or equivalent) should be able to order TPE, but this is likely to be dependent on specific policies of the hospital or medical group that the doctor is affiliated with. The equipment needed to perform TPE is likely to be available in any large hospital, but this may mean that there can be access problems for patients in rural areas.
TPE requires specialized equipment that is typically only available in large hospital setting. Since our suggested protocol requires about 16 TPE treatments per year, travel time to and from the hospital can be a significant barrier for patients who are in rural settings or do not have easy access to the hospital.

Most rheumatologists have little or no experience with TPE since it is not commonly used with rheumatological diseases. Because of this, they often have major misconceptions about TPE, for example: 1) It is too dangerous to use except as a last resort, 2) you can’t do TPE without a catheter and catheters have high infection risk, and 3) you can have a major allergic reaction from replacement plasma, and 4) my personal favorite: “It’s too new and experimental!”

This is a quote from a physician after a patient asked him to read the published research on TPE so they could discuss whether or not it made sense to consider trying it: “I’m not going to read the research because I know it doesn’t work”. Time for a new physician?

We have a lot of additional information on TPE in the Research section of our website, including a more detailed discussion of the background research on abnormal blood rheology in systemic sclerosis. In addition to the review paper and the case report discussed earlier, there are two other documents that can be very helpful for any clinicians who are considering trying TPE with suitable patients.

If a clinician is interested in trying TPE with a suitable patient, it is useful to have a starting point for figuring out both the treatment protocol and how to monitor changes in symptoms and basic laboratory markers. We have prepared a document for clinicians that outlines a suggested treatment protocol for a one-year trial of plasma exchange using the research-based pulsed protocol described in the long-term case report discussed earlier. It includes suggested subjective and objective measures that can be used to assess how well the treatments are working.

The Guidelines document is available in the Clinician Resources section of our website.

It is completely normal for a patient to feel anxious when starting a treatment like TPE. They will commonly be concerned about how painful it will be to insert the IV needles and also how they will feel during and after the procedure.

In order to try to reduce this anxiety and prepare the patient for a more comfortable and successful TPE experience, I worked with the head nurse at the infusion center at the University of Wisconsin Hospital to create a document titled “Therapeutic Plasma Exchange: A Guide for Newbies.” It explains the process of TPE, how to prepare for a treatment, what it will feel like during and after, and possible short-term side effects and how to reduce them. It is available through our website. I would encourage both...
In summary, the published research suggests that long-term TPE may be a low-risk way to control and potentially reverse systemic sclerosis symptoms in some patients. While TPE has been tried with more than 450 patients according to the studies we reviewed, it is important to note that the quality of many of the studies, especially the early ones, was not very high. We also do not have a clear understanding of which patients would most benefit from TPE. However, it is clear that starting TPE fairly early in the disease process is likely to lead to the best outcomes.

There is a clear need and justification for a well-designed, randomized controlled trial of TPE using modern equipment and modern venous access techniques. It is also important to try to better understand the mechanisms of action of TPE, as this might lead to other potential interventions, including pharmaceutical ones, that might be easier and cheaper alternatives to TPE.

Thank you! If you have any questions, please feel free to contact me at eharris@sclerodermainfo.org.