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Suggested Protocol for a One-Year Trial of Therapeutic Plasma Exchange for Treating Patients with Limited Systemic Sclerosis

Introduction

The purpose of this document is to provide background information for physicians and patients who have reviewed the research literature on the use of therapeutic plasma exchange (TPE) to treat systemic sclerosis (SSc) and made the determination that this may be an appropriate treatment option. While this is not intended to be a formal research proposal, it is hoped that by following a standardized protocol for administering TPE, as well as including a basic set of objective measures during the trial of TPE, we may be able to glean important information that can be used as the basis for future well-designed clinical trials of TPE for treating patients with SSc.

Background

TPE is a procedure used to treat a variety of diseases and conditions where it is believed or documented that some type of circulating blood component such as autoantibodies or abnormal proteins is causing or contributing to the disease process. TPE is done by mechanically separating blood components and replacing the liquid part of the blood (plasma) with a plasma substitute with the specific goal of temporarily reducing any blood circulating harmful components.

TPE is usually done in a hospital setting but on an outpatient basis. Generally speaking, side effects are very mild and TPE has an excellent safety profile. A typical TPE procedure takes two to three hours.

Therapeutic plasma exchange (TPE) has been used to treat patients with systemic sclerosis (SSc) since 1978. A recent paper [1] reviewed 40 published articles on the use of TPE to treat patients with different variants of SSc, ranging from case reports to full clinical trials. While many of these studies have major limitations, the overall data suggests that long-term TPE may be a low-risk treatment option for at least a subset of patients with SSc.

Abbreviations	
ACA	anticentromere antibody
dcSSc	diffuse cutaneous systemic sclerosis
DLCO	diffusing capacity of carbon monoxide
DLCO/VA	diffusing capacity divided by the alveolar volume
ESR	erythrocyte sedimentation rate
HSCT	hematopoietic stem cell transplant
lcSSc	limited cutaneous systemic sclerosis
PAH	pulmonary artery hypertension
PFT	pulmonary function test
RBC	red blood cell (erythrocyte)
SHAQ	Scleroderma Health Assessment Questionnaire
SSc	systemic sclerosis
TPE	therapeutic plasma exchange
WBV	whole blood viscosity

While many of the studies focused on studying the effects of a limited course of TPE or longer term use of TPE in concert with standard immunosuppressant therapy, a very recent case report [2] followed a patient diagnosed in early 1990 with anticentromere antibody (ACA) positive, limited systemic sclerosis treated solely with regular TPE treatments beginning in late 1993 and continuing to the present day. The patient went

into remission after about two years of regular TPE treatments and has remained symptom free for the past 20 years, except for very mild residual Raynaud's.

TPE is known to temporarily reduce plasma circulating levels of potential pathogenic factors such as autoantibodies, cytokines, or other abnormal proteins. In addition, TPE has also been shown to reduce abnormally elevated blood viscosity and red blood cell aggregation commonly seen in SSc [3,4,5,6].

A full clinical trial of TPE to treat SSc is in early stages of planning, but it will be at least several years before results from such a trial will be available (contact the author for more information on the design of the proposed clinical trial). However, in the event that physicians and patients make the decision to try TPE on an individual basis (prior to the results of a future clinical trial being published), it makes sense to try to learn as much as possible from any such individual trials.

The main purpose of this document is to describe the protocol that was used in the recent case report referenced above [2], including a brief discussion of the background research that lead to this particular protocol being selected. The same protocol will also be used in the proposed future clinical trial. If clinicians choose to follow this protocol in their own initial individual patient trials of TPE, this will greatly facilitate data gathering for future analysis and reporting.

Any patients considering a trial of TPE should be fully aware that TPE is currently considered an experimental procedure for treating SSc; they should carefully review and discuss with their physicians the potential risks involved in this treatment approach before embarking on a trial of TPE.

Patient Selection Criteria in Proposed Clinical Trial

The proposed initial clinical trial mentioned above will be limited to patients with ACA-positive, limited systemic sclerosis (lcSSc) who have no major internal organ involvement or other risk factors that would contraindicate TPE. While this has not been studied in the research literature, anecdotal reports suggest that TPE may be more effective in patients with lcSSc than in patients with diffuse systemic sclerosis (dcSSc) (at least using the TPE treatment frequency suggested here). The initial study design restriction is designed to increase the likelihood that a clear determination can be made on the efficacy of TPE in this subset of the SSc patient population. If TPE is determined to be an effective treatment option for patients with lcSSc, follow-up research would need to be done to determine if TPE is similarly effective for patients with dcSSc.

Suggested Treatment and Testing Protocol

Recommended TPE Protocol (See Background Discussion Below)

The basic recommended TPE treatment protocol is one TPE treatment per week for four weeks followed by eight weeks of rest. This is to be repeated for a total of 16 TPE treatments over a 48-week period. Each TPE treatment should be one volume exchange using 5% albumin as the plasma substitute. The rational and background research for this "pulsed" TPE treatment protocol is discussed below.

Recommended Baseline and Concurrent Testing

Before starting TPE, the patient's antibody type should be identified by appropriate antibody testing. We also suggest getting a baseline pulmonary function test (PFT) if this has not been done in the previous six-month time period, as well as a baseline CBC, chemistry panel, and UA. We also suggest that the patient fill out the Scleroderma Health

Assessment Questionnaire (SHAQ) just before starting TPE. (A copy of the SHAQ is available from the author of this document.) These measures will be repeated at the end of the TPE trial.

Since previous research [3,4,5,6] has shown that TPE leads to significant reductions of both elevated blood viscosity (thickness/stickiness) and red blood cell aggregation (clumping) commonly seen in patients with SSc, directly monitoring potential changes in whole blood viscosity and red blood cell aggregation would be ideal. Unfortunately, red blood cell aggregation cannot easily be measured outside of a laboratory setting and whole blood viscosity (WBV) can be quite expensive*. However, erythrocyte sedimentation rate (ESR) is strongly correlated with red blood cell aggregation [7] and can be used as a good proxy measure for RBC aggregation. A "corrected" ESR can be calculated that factors in hematocrit levels (CBC), an important correction when looking for changes in ESR over time.

Pulmonary function tests are typically recommended for patients with SSc on at least an annual basis. ACA-positive lcSSc patients have an increased risk of developing pulmonary artery hypertension (PAH) over the long-term. Recent research suggests that reduction in two measures of lung functioning can be predictors of an increased risk of developing PAH in the future: DLCO (diffusing capacity of carbon monoxide) and DLCO/VA (diffusing capacity divided by the alveolar volume). Monitoring changes in these two measures by period PFT testing will be useful in determining if TPE has any effect on these important future risk indicators.

Suggested 48-week TPE Protocol:

Week	Procedure/Test	TPE	Notes
Pre-TPE	**SHAQ, PFT, Chem Panel, UA**		
1	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV at start of TPE treatment
2		X	
3		X	
4	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV after end of TPE treatment
5-12			Rest
13	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV at start of TPE treatment
14		X	
15		X	
16	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV after end of TPE treatment
17-24			Rest
25	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV at start of TPE treatment
26		X	
27		X	
28	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV after end of TPE treatment
29-36			Rest
37	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV at start of TPE treatment
38		X	
39		X	
40	ESR, CBC, WBV*	X	Draw ESR, CBC, and WBV after end of TPE treatment
41-48			Rest
49: Post-TPE	**SHAQ, PFT, Chem Panel, UA**		

SHAQ: Scleroderma Health Assessment Questionnaire; PFT: pulmonary function test; UA: urinalysis; ESR: erythrocyte sedimentation rate; CBC: complete blood count; *WBV: whole blood viscosity (optional)

Frequently Asked Questions

1. **In the case study [2], the patient was taking no concurrent systemic medications. If the patient is currently taking systemic medications such as steroids, methotrexate or other immunosuppressants, do these medications need to be stopped before starting a trial of TPE?**

   No. TPE is commonly used as an adjunct treatment along with standard immunosuppressant therapies. If the patient is taking concurrent systemic medications, ideally the doses may stay constant or decrease during the TPE trial period. This will allow a more accurate determination of whether or not any clinical improvements are likely to be from the addition of TPE treatments. If, however, the patient responds well to the initial TPE trial period, and the decision is made to continue TPE, it may be worth considering whether or not to try gradually reducing other medications to see if they are still required at initial dosages, or at all.

2. **What is the safety profile of TPE? Are there any contraindications for trying TPE?**

   The overall safety profile for long-term use of TPE is excellent. The most common side effects are very short term, e.g., hypotension (low blood pressure) or fatigue during or for a few hours following a treatment. A recent study [8] reviewed the efficacy and safety of TPE in 317 patients with 2730 procedures over an 11-year period. Observed adverse events occurred in 3% of the procedures. In all cases the adverse events were mild, and the patients were able to complete the scheduled TPE treatments. Another study [9] reviewed 4857 TPE treatments. The overall incidence of complications was 4.75%, almost entirely minor. There were five cases of severe allergic reactions (0.12%), all of which occurred with the use of fresh frozen plasma rather than the albumin plasma substitute recommended in this document.

   Also, patients may have other conditions that make TPE an unsuitable treatment option. For example a recent study [10] suggests that TPE is contraindicated for the following patients:

   - Patients who are actively septic or are hemodynamically unstable
   - Patients who have allergies to fresh frozen plasma or albumin depending on the type of plasma exchange
   - Patients with heparin allergies should not receive heparin as an anticoagulant during plasmapheresis
   - Patients with hypocalcemia are at risk for worsening of their condition because citrate is commonly used to prevent clotting and can potentiate hypocalcemia

   In addition, in patients with significant renal disease, TPE has not been found to be effective, and there can be more serious complications from TPE in this patient population, thus making them unsuitable for TPE.

   For these reasons, it is strongly recommended that TPE be administered in a facility with experienced staff who perform TPE on a regular basis. It is also important that the facility is equipped to deal with the very rare but potentially serious risks cited above.

3. **If TPE is beneficial during the one-year trial period, how long does it need to be continued?**

   Since SSc is a chronic disease, any treatment, including TPE, immunosuppression, or interventions that target the fibrotic processes in SSc, will need to be continued on a permanent and regular basis in order to provide the maximum possible benefit.

4. **I have heard that you can't do long-term TPE without some sort of central access port? Can you comment on this?**

   About 75% of TPE treatments can be performed using regular peripheral venous access [11]. For patients with venous access problems, the use of new vein illumination technology such as VeinViewer™ and AccuVein™ should significantly reduce venous access problems when more widely adopted. For patients who experience anxiety focused around the potential pain of IV insertion, studies have shown that both intradermal buffered lidocaine 1% and bacteriostatic normal saline are very effective in reducing the pain during IV catheter insertion [12].

   For patients who cannot undergo normal peripheral venous access, a number of alternatives are available. Central catheters are not a good option for most patients for long-term TPE due to the significant risk of infection. Alternatives such as surgically created fistulas or implantable vascular-access devices (ports), such as PowerPorts™ or Vortex™, may be better options for very-long term use of TPE, if peripheral venous access cannot be used.

   Patients often experience significant anxiety when first undergoing TPE. This normal anxiety can greatly increase problems with venous access. Because of this, we have prepared a printable handout titled "Therapeutic Plasma Exchange: A Guide for Newbies" that is intended to help patients be better prepared for and thus less anxious about starting TPE treatments (available from the author).

5. **My understanding is that TPE is very expensive and insurance coverage is not available to cover the cost.**
   A 2011 study [13] did an analysis of the cost of TPE and determined that each treatment cost a little under $1200 when TPE was performed using albumin. Based on this estimate, the actual cost of one year of TPE treatments using the suggested pulsed protocol (16 treatments total) would be approximately $20,000. For comparison, a recent study of the annual cost of modern biologic drugs now commonly used to treat rheumatoid arthritis and other autoimmune conditions [14] indicated that the lowest price biologic – Humira (adalimumab) – was about $21,000 per year. Other biologics were somewhat higher. This suggests that annual costs for long-term TPE, while significant, are similar to standard pharmacological options used for other autoimmune diseases. 2015 average Medicare reimbursement rates for TPE are about $1140 plus the cost of albumin, which varies depending on the size of the patient. However, it is understood that hospitals and clinics may charge more than this Medicare reimbursement amount.

   The issue of whether or not insurance will cover the cost is uncertain. TPE is currently classified as Category III by the American Society for Apheresis: "Optimum role of apheresis therapy is not established. Decision making should be individualized." This kind of language indicating that a treatment is “not established” generally means that insurance companies are likely to view it as experimental and will not cover the cost. On the other hand, when the patient in the case report [2] turned 65 four years ago,

Medicare covered the cost of the TPE treatments without requiring any additional documentation. The formal Medicare guidelines for using TPE [15] indicate that TPE is an approved procedure for: "Treatment of life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy." Since some insurance companies specifically follow Medicare guidelines for coverage of non-standard treatments, it is possible that these companies will (after suitable prodding) agree to cover the cost of TPE treatments.

Background Research for Pulsed TPE Protocol

TPE has been tried as a treatment for systemic scleroderma since 1978. The usual rationale and the primary post hoc explanation for any benefits seen from TPE is that TPE temporarily reduces the levels of circulating pathological factors (e.g., autoantibodies or immune complexes, cytokines or adhesion molecules) that are associated with SSc.

However, the treatment protocol used in the very long-term case report is based on a completely different SSc pathogenesis model that is explained in some detail in the TPE review article [1] mentioned above. Many studies have documented increased blood viscosity in SSc and, when examined in detail, the specific nature of the elevated blood viscosity is primarily from red blood cell aggregation [4,5,16,17,18]. A 1979 paper [19] suggests that all symptom development in scleroderma stems from repeated damage to the endothelial lining of the microvascular system. Our proposed SSc pathogenesis model suggests that RBC aggregation, commonly seen in SSc, is the direct trigger for this endothelial damage.

Studies [4,5,20] have demonstrated that a series of four weekly TPE treatments substantially reduces the abnormal RBC aggregation and elevated whole blood viscosity seen in the majority of patients with SSc. In addition, these improved blood rheology effects last for three months or longer following the last TPE treatment. Based on these observed data, the decision was made to use a "pulsed" TPE protocol designed to normalize blood rheology using a series of four weekly TPE treatments, followed by an eight-week resting period. The basic assumption of the pulsed TPE protocol is that while blood rheology will slowly return towards pre-treatment levels during the eight-week inter-treatment resting interval, the levels of RBC aggregation during that inter-treatment period will be low enough to result in little or no further endothelial damage during the resting period.

Even assuming this TPE protocol is successful, since SSc is a chronic disease, regular TPE treatments will need to be continued permanently to remain effective. The case report [2] demonstrated that stopping TPE led to the return of symptoms after about six months.

One other note regarding the treatment protocol and symptom reduction: while significant symptom improvements were reported in the case report after one year of TPE treatments (16 treatments), it took about two years for the patient to go into nearly full remission, including elimination of all GERD symptoms and improved lung functioning on PFT. This suggests that while it is possible that some early organ damage may be reversible, it will take a significant period of time for this recovery to take place.

Summary

Currently, therapeutic plasma exchange is rarely used in the United States to treat patients with SSc. (It is actually used more frequently in Europe and in Italy it is a standard and approved treatment option.) A newly published case report [2] suggests that long-term TPE may be an effective treatment option that physicians may want to consider

trying with SSc patients, especially if the patient has a similar diagnosis and symptom profile to the patient in the case report.

A well-designed, prospective clinical trial will be needed in order to evaluate whether or not TPE is a beneficial treatment option for SSc patients. However, in the event that a clinician decides to try TPE with one or more of their SSc patients, by having a standardized protocol for administering TPE and a core set of recommended objective measures, we will be better able to pool and analyze data that will be helpful in determining if TPE is a potential treatment option that should be studied formally.

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Contact Information

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