



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

Introduction

The purpose of this document is to provide background information for clinicians 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 clinical trials of TPE for treating patients with SSc.

A concise summary of the overall protocol, including suggested patient selection criteria, pre-, during-, and post-treatment testing, and TPE treatment protocol is included in Appendix A of this document.

Background

TPE is a procedure used to treat numerous disorders where removing plasma (which often contains molecules that trigger symptoms and signs of these disorders) has proven to be curative or highly beneficial.

TPE is usually done in a hospital setting 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.

TPE has been used to treat patients with systemic sclerosis (SSc) since 1978. A comprehensive TPE/SSc review paper has been submitted for publication [1] (contact the author for a copy of the current manuscript). While many of these studies have significant limitations, the overall data suggest that long-term

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

TPE may be a low-risk treatment option for at least a subset of patients with SSc. While most of these studies focused on studying the effects of either a limited course of TPE or longer-term use of TPE in concert with standard immunosuppressant therapy, a recent case report [2] followed a patient diagnosed in early 1990 with anticentromere antibody (ACA) positive, limited systemic sclerosis who was 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 molecules. In addition, TPE has been shown to reduce abnormally elevated blood viscosity and red blood cell aggregation commonly seen in SSc [3,4,5,6].

The main purpose of this document is to suggest a possible TPE protocol for a one-year trial of TPE, based on the protocol that was used in the recent case report referenced above [2]. A brief discussion of the background research that led to this particular protocol is included later in this document. It is our hope that SSc patients and clinicians who are considering TPE as a treatment option may find our suggestions useful.

Any patients considering a trial of TPE should be fully aware that TPE is currently considered an experimental procedure for treating SSc in the US. Medicare and some US healthcare companies cover TPE as an available treatment option for SSc patients who are unresponsive to conventional therapy [7]. The American Society for Apheresis currently classifies TPE for treating systemic sclerosis as a Category III treatment: "Optimum role of apheresis therapy is not established. Decision making should be individualized." [8].

Patient Selection Criteria

TPE has been used to treat diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) patients (also patients with Mixed Connective Tissue Disease) with positive results in the majority of patients [1]. However, several published studies [9,10,11] have documented that TPE is not effective in late stages of SSc, especially for patients in scleroderma renal crisis. The consensus was that for TPE to be most effective, it should be started relatively early in the disease process. However, there has not been any research that clearly defines what this means. The long-term case report [2] documented symptom reversal, including improvement in lung functioning, over a several-year time period. At the time that regular TPE treatments initiated (late 1993), the patient had exhibited Raynaud's symptoms for eight years and was almost four years post diagnosis.

Recommended TPE Treatment and Testing Protocols

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 42-week period. Each TPE treatment should be a one volume exchange using 5% albumin as the plasma substitute. The rationale and background research for this "pulsed" TPE treatment protocol are discussed below.

Pre-, During-, and Post-Treatment Assessments

Pre-Treatment Assessments

- **Antibody Identification.** Before starting TPE, the patient's antibody type should be identified by appropriate antibody testing. While TPE has been used to treat lcSSc and dcSSc patients with several different scleroderma-specific antibodies [1], a key unanswered question is whether different variants of SSc respond differently to TPE. Documenting the antibody type before starting a trial of TPE may help to answer this key question.

Note: there are known false positive issues with Scl-70 antibody testing using ELISA and Multiplex testing [12]. If the patient is diagnosed with dcSSc with positive Scl-70 antibodies based on ELISA or Multiplex testing, we suggest that more reliable testing methods such as immunodiffusion be used to confirm this antibody result. Contact the author of this paper for more information.

- **Scleroderma Health Assessment Questionnaire (SHAQ).** A copy of the SHAQ is included in Appendix B.
- **Pulmonary Function Tests (PFT)** are typically recommended for patients with SSc on at least an annual basis as lung involvement is very common in all variants of SSc. Monitoring changes in key PFT measures, such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), pre and post the one year trial of TPE may help to determine objectively if TPE is having any effect on pulmonary symptoms.
- **CBC, chemistry panel, and UA.**
- **Erythrocyte Sedimentation Rate (ESR).** 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) testing is quite

expensive*. However, erythrocyte sedimentation rate (ESR) is strongly correlated with red blood cell aggregation [13] and it may be a proxy measure for monitoring changes in 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.

ESR testing can be done by a variety of different methods that have different normal ranges (*e.g.*, Wintrobe, Westergren). For this reason, it is important to document the testing method used for ESR testing and, if possible, the same testing method should be used for all ESR testing during the one-year trial period.

- **Nailfold Capillaroscopy** is being increasingly used as a method for evaluating disease activity in patients with SSc [14]. Nailfold capillary abnormalities are steadily progressive in SSc. In earliest stages, nailfold imagery shows a few enlarged capillaries but the overall capillary distribution is relatively normal. As the disease progresses, you see increasing giant capillaries and hemorrhages and some capillary loss. In late stages, there is severe capillary loss and extensive disorganization of the remaining capillaries. [15]

If it is possible, we strongly encourage doing pre-treatment and post-treatment nailfold capillary image capture, preferably at a 200x level of magnification. In early stages, magnification levels of 200x are required to see changes in individual capillaries but at later stages, magnification in the 10x to 20x level can be used to provide an overall view of capillary patterns. Typically, the best view is the little and ring finger of the non-dominant hand [16]. Since capillary deterioration is normally steadily progressive in SSc, any improvements in nailfold capillaries at the end of the TPE trial period would suggest a beneficial effect from the treatments.

Note: While it common to use the Modified Rodnan Skin Score (MRSS) as an outcome measure in clinical trials of SSc treatments, we have chosen to exclude this as a recommended measure for this suggested trial of TPE. About two-thirds of dcSSc patients show significant spontaneous improvement in skin thickness starting a year or two after initial diagnosis for reasons that are not fully understood. It is important to note, however, that there are no corresponding spontaneous improvements in internal disease markers (17). This means that if a pre-post treatment study of early stage dcSSc patients shows improvements in MRSS following TPE, it is not necessarily the case that improvements can be attributed to the use of TPE (or any other intervention).

* The Scleroderma Education Project has limited funding available to cover the cost of WBV testing. Contact the author of this document for more information.

During-Treatment Assessments

- **Scleroderma Health Assessment Questionnaire (SHAQ).** The patient should fill out a new SHAQ at the start of each treatment cycle.
- **ESR and CBC.** These should be drawn at the start of each TPE session.

Post-Treatment Assessments

(One week after the last TPE; at one-year anniversary of starting TPE)

- **Scleroderma Health Assessment Questionnaire (SHAQ).**
- **Pulmonary Function Test (PFT).**
- **CBC, chemistry panel, and UA.**
- **Erythrocyte Sedimentation Rate (ESR).**
- **Nailfold Capillaroscopy**

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 should either 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 [18] 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 [19] 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 [20] 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 [21]. 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 [22].

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 [23] did an analysis of the cost of TPE and determined that each treatment cost a little under \$1,200 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 [24] indicated that the lowest price biologic – Humira (adalimumab) – was about \$51,000 per year. Some newer immunomodulating drugs for treating autoimmune disorders cost >\$100,000 per year. This suggests that annual costs for long-term TPE, while significant, are similar to standard pharmacological options used for other autoimmune diseases and substantially lower than the costs of newer possible treatments whose effects in SSc are largely unknown. 2015 average Medicare reimbursement rates for TPE are about \$1,140 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. The current classification of TPE as a category III treatment by the American Society for Apheresis 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, Medicare covered the cost of the TPE treatments without requiring any additional documentation. 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.

6. How can we evaluate the effectiveness of the TPE trial at the end of the one-year trial period?

With any single-subject open label experimental treatment such as is proposed in this document, placebo effects are very likely. While it is important to include subjective measures such as the Scleroderma Health Assessment Questionnaire (SHAQ) as pre-treatment and post-treatment measures, it is more important to focus on objective markers. Unlike diseases such as multiple sclerosis or lupus, SSc is a disease which is steadily progressive and does not go into remission without an intervention. Because of this, any objective changes in laboratory markers or symptoms following the introduction of TPE are likely to be a result of the intervention as long as there are no confounding co-treatments.

A commonly reported finding in 16 out of the 46 papers reviewed [1] was that a single course of a small number of weekly TPE treatments (typically four) had major effects on both Raynaud's Phenomenon (RP) and digital ulcers (DU), as well as blood flow and microvascular patency. For most patients, RP disappeared or was significantly improved, and even long-standing digital ulcers began to heal.

If the long-term TPE case report [2] of a patient with lcSSc is representative, at the end of one year you would be likely to have improvements in symptoms such as GERD and Raynaud's that would be reflected in improved SHAQ scores. However, symptoms such as GERD and even frequency of Raynaud's attacks are subjective measures. Objective measures of changes in GI functioning can be considered, including pre- and post-treatment esophageal manometry to measure lower esophageal sphincter pressure and esophageal motility.

It is very likely that measures of lung functioning such as DLCO or FEV would show little, if any, change over a one-year time period. At the two-year point in the case study [2], DLCO showed slight improvement over pre-treatment levels. Significant improvements in DLCO were not seen until about four years of regular TPE treatments. Several of the studies that were described in the TPE review paper [1] suggest that measures such as DLCO and FEV are likely to stabilize but not improve after one year of TPE treatments.

Nailfold capillary imagery will be a useful assessment tool at the one-year marker. One study documented improvements in nailfold capillaries after one year of combined TPE and IVIG [25]. If there are clear improvements in this measure, this suggests that TPE is having a beneficial systemic effect.

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 [5,6,26,27,28]. A 1979 paper [29] 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, may be a trigger for this endothelial damage.

Studies [5,6,30] 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. Improvements in lung functioning took even longer. 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 choose to consider trying with SSc patients, especially if the patient has a similar diagnosis and symptom profile to the patient in the case report.

Well-designed, prospective clinical trials are needed in order to evaluate clinical benefits of TPE in different forms of SSc. However, until the results of these future trials are known, it is our hope that the standardized TPE protocol and assessment measures suggested in this document may be useful for patients and clinicians who are considering trying TPE as a treatment option.

Acknowledgements

The author wishes to thank Patrick M Moriarty MD (University of Kansas Medical Center), Allan L. Metzger, MD (RDL Reference Laboratory), Herbert J Meiselman ScD (Keck School of Medicine, Univ. of Southern California), Miroslav Malkovsky MD PhD (University of Wisconsin, Madison), and Alan Bridges MD (University of Wisconsin, Madison) for their invaluable assistance in the preparation of this document.

Disclosure

The author of this document is also the lead author of the above referenced TPE review paper [1] and case report [2]. He is also the patient referenced in the case report.

Research Note

As part of a planned study on plasma factors in SSc, we are interested in obtaining a small quantity (20-50 milliliters) of discarded plasma from the first TPE treatment. It would need to be stored in a Falcon or equivalent centrifuge tube and shipped frozen to the research lab located in Madison, WI. All costs for specimen handling and shipping would be paid for by the Scleroderma Education Project. Please contact the author of this of this paper for more information.

Contact Information

If you have any comments or questions or are planning a trial of TPE, please contact the author:

Edward S Harris, CEO
Scleroderma Education Project
eharris@sclerodermainfo.org

Fellow, Dept. of Medicine
University of Wisconsin, Madison
eharris5@wisc.edu

References

1. Harris ES, Meiselman HJ, Moriarty PM, Metzger A, Malkovsky M. Therapeutic plasma exchange for the treatment of systemic scleroderma: a comprehensive review and analysis. Manuscript currently in review. Contact the author for a copy.
2. Harris E, Meiselman H, Moriarty P, Weiss J. Successful long-term (22 Year) treatment of limited scleroderma using therapeutic plasma exchange: Is blood rheology the key? *Clin Hemorheol Microcirc.* 2017;65:131-136. doi:10.3233/CH-16140. Download link: <http://www.sclerodermainfo.org/pdf/CHM-Case-Report-Manuscript-US.pdf>
3. Dodds AJ, O'Reilly MJ, Yates CJ, Cotton LT, Flute PT, Dormandy JA. Haemorrhological response to plasma exchange in Raynaud's syndrome. *British Medical Journal* 1979; 2(6199): 1186–1187.
4. Weber H, Schmid-Schonbein H, Lemmens HA. Plasmapheresis as a Treatment of Raynaud's Attacks: Microrheological Differential Diagnosis and Evaluation of Efficacy. *Clinical Hemorheology* 1985; 5; 85-97.
5. Jacobs MJ, Breslau PJ, Slaaf DW, Reneman RS, Lemmens JA. Nomenclature of Raynaud's phenomenon: A capillary microscopic and hemorheologic study. *Surgery* 1987; 101; 136-145.
6. Jacobs MJ, Jorning PJ, von Rhede van der Kloot EJ, Kitslaaar PJ, Lemmen HA, Slaaf DW, Reneman RS. Plasmapheresis in Raynaud's phenomenon in systemic sclerosis: a microcirculatory study. *International Journal of Microcirculation: Clinical and Experimental* 1991; 10; 1-11.
7. National Coverage Determination (NCD) for Apheresis (Therapeutic Pheresis) (110.14).
8. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher.* 2016;31(3):149-338. doi:10.1002/jca.21470.
9. Guillevin L, Leon A, Levy Y, et al. Treatment of progressive systemic sclerosis with plasma exchange. Seven cases. *Int J Artif Organs.* 1983;6(6):315-318.
10. Capodicasa G, De Santo NG, Galione A, et al. Clinical effectiveness of apheresis in the treatment of progressive systemic sclerosis. *Int J Artif Organs.* 1983;6 Suppl 1:81-86.
11. Kfoury Baz EM, Mahfouz RA, Masri AF, Jamaledine GW. Thrombotic thrombocytopenic purpura in a case of scleroderma renal crisis treated with twice-daily therapeutic plasma exchange. *Ren Fail.* 2001;23(5):737-742.

12. Meier S, Mikuls TR. Positive Predictive Value of Anti-Centromere and Anti-Scl-70 Antibody Multiplex Assays in a Rheumatology Practice Setting. *Arthritis Rheum.* 2011;63(Suppl 10):694.
13. Baskurt O, Neu B, Meiselman HJ. *Red Blood Cell Aggregation.* Boca Raton: CRC Press 2011.
14. Sambataro D, Sambataro G, Zaccara E, et al. Nailfold videocapillaroscopy microhaemorrhage and giant capillary counting as an accurate approach for a steady state definition of disease activity in systemic sclerosis. *Arthritis Res Ther.* 2014;16(5):462. doi:10.1186/s13075-014-0462-
15. Cutolo M, Matucci Cerinic M. Nailfold capillaroscopy and classification criteria for systemic sclerosis. *Clin Exp Rheumatol.* 2007;25(5):663-665.
16. Etehad Tavakol M, Fatemi A, Karbalaie A, Emrani Z, Erlandsson B-E. Nailfold Capillaroscopy in Rheumatic Diseases: Which Parameters Should Be Evaluated? *Biomed Res Int.* 2015;2015:1-17. doi:10.1155/2015/974530.
17. Steen VD, Medsger TA. Improvement in skin thickening in systemic sclerosis associated with improved survival. *Arthritis Rheum.* 2001;44(12):2828-2835.
18. Cid J, Carbassé G, Andreu B, Baltanás A, Garcia-Carulla A, Lozano M. Efficacy and safety of plasma exchange: an 11-year single-center experience of 2730 procedures in 317 patients. *Transfus Apher Sci.* 2014;51(2):209-214. doi:10.1016/j.transci.2014.08.018.
19. Basic-Jukic N, Kes P, Glavas-Boras S, Brunetta B, Bubic-Filipi L, Puretic Z. Complications of Therapeutic Plasma Exchange: Experience With 4857 Treatments. *Ther Apher Dial.* 2005;9(5):391-395. doi:10.1111/j.1744-9987.2005.00319.x.
20. Malchesky PS. Therapeutic Apheresis: Why? *Ther Apher Dial.* 2015;19(5):417-426. doi:10.1111/1744-9987.12353.
21. Khatri B, Kramer J. Vascular access for therapeutic plasma exchange. *Muscle Nerve.* 2013;48(4):624. doi:10.1002/mus.23873.
22. Deguzman ZC, O'Mara SK, Sulo S, Haines T, Blackburn L, Corazza J. Bacteriostatic normal saline compared with buffered 1% lidocaine when injected intradermally as a local anesthetic to reduce pain during intravenous catheter insertion. *J Perianesth Nurs.* 2012;27(6):399-407. doi:10.1016/j.jopan.2012.08.005.
23. Winters JL, Brown D, Hazard E, Chainani A, Andrzejewski C. Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain-Barré syndrome. *BMC Health Serv Res.* 2011;11:101. doi:10.1186/1472-6963-11-101.

24. Howe A, Eyck L Ten, Dufour R, Shah N, Harrison DJ. Treatment patterns and annual drug costs of biologic therapies across indications from the Humana commercial database. *J Manag care Spec Pharm*. 2014;20(12):1236-1244. <http://www.ncbi.nlm.nih.gov/pubmed/25443517>.
25. Szekanecz Z, Aleksza M, Antal-Szalmás P, et al. Combined plasmapheresis and high-dose intravenous immunoglobulin treatment in systemic sclerosis for 12 months: follow-up of immunopathological and clinical effects. *Clin Rheumatol*. 2009;28(3):347-350. doi:10.1007/s10067-008-1062-2.
26. McGrath MA, Peek R, Penny R. Blood hyperviscosity with reduced skin blood flow in scleroderma. *Annals of the Rheumatic Diseases*. 1977; 36(6): 569–574.
27. Vayá A, Todolí J, Calvo J, Romagnoli M, Ricart JM. Haemorheological profile in patients with systemic sclerosis. *Clin Hemorheol Microcirc*. 2008; 40(3):243-248.
28. Volkov S, Utset TO, Schmitz A, Ellman M, Cao D SN. Whole Blood Viscosity (WBV) and Digital Ulcers in Scleroderma Patients. In: ACR/AHRP Annual Scientific Meeting. 2006: F56.
29. Kahaleh MB, Sherer GK, LeRoy EC. Endothelial injury in scleroderma. *Journal of Experimental Medicine*. 1979; 149(6); 1326-1335.
30. von Rhede van der Kloot E J H, Jacobs M J H M, Weber H LHAJ. Plasma Filtration in Patients with Raynaud's Phenomenon. *Clin Hemorheol Microcirc*. 1985;5.

Appendix A

Recommended Patient Selection, TPE, and Testing Protocols

Patient Selection

- Early stage lcSSc, dcSSc, or MCTD

Exclusion Criteria

- Patients who are actively septic or are hemodynamically unstable
- Patients who have allergies to albumin
- 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

TPE Protocol

- 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 42-week period
- Each TPE treatment should be a one volume exchange using 5% albumin as the plasma substitute

Testing Protocol

Week	Procedure/Test	TPE	Notes
Pre-TPE	SHAQ, PFT, Chem panel, UA, nailfold capillaroscopy image capture		
1	ESR, CBC	X	Draw blood for ESR, CBC at start of TPE treatment
2		X	
3		X	
4		X	
5-12			Rest
13	ESR, CBC, SHAQ	X	Draw blood for ESR, CBC at start of TPE treatment
14		X	
15		X	
16		X	
17-24			Rest
25	ESR, CBC, SHAQ	X	Draw blood for ESR, CBC at start of TPE treatment
26		X	

27		X	
28		X	
29-36			Rest
37	ESR, CBC, SHAQ	X	Draw blood for ESR, CBC at start of TPE treatment
38		X	
39		X	
40		X	
41			Rest
42: Post-TPE: One-week after last TPE	ESR, CBC, SHAQ, PFT, Chem Panel, UA, nailfold capillaroscopy image capture		
52: Follow-up	ESR, CBC, SHAQ, PFT, Chem Panel, UA, nailfold capillaroscopy image capture		

SHAQ: Scleroderma Health Assessment Questionnaire; PFT: pulmonary function test; UA: urinalysis; ESR: erythrocyte sedimentation rate; CBC: complete blood count

Appendix B

Scleroderma Health Assessment Questionnaire

In this section, we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add comments.

Please check the one response that best describes your usual abilities IN THE PAST SEVEN DAYS.

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dressing and Grooming				
Are you able to dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
Are you able to shampoo your hair?	_____	_____	_____	_____
Arising				
Are you able to stand up from an armless straight chair?	_____	_____	_____	_____
Are you able to get in and out of bed?	_____	_____	_____	_____
Eating				
Are you able to cut your meat?	_____	_____	_____	_____
Are you able to lift a full glass to your mouth?	_____	_____	_____	_____
Are you able to open a new milk carton?	_____	_____	_____	_____
Walking				
Are you able to walk outdoors on flat ground?	_____	_____	_____	_____
Are you able to climb up five stairs?	_____	_____	_____	_____

Please check any AIDS or DEVICES that you usually use for these activities:

_____ Cane	_____ Devices for dressing (button hook, zipper pull, long handled shoe horn, etc.)
_____ Walker	_____ Built up or special utensils
_____ Crutches	_____ Special or built-up chair
_____ Wheelchair	_____ Other (specify: _____)

Please check any categories for which you usually need ASSISTANCE FROM ANOTHER PERSON

_____ Dressing and grooming

_____ Eating

_____ Arising

_____ Walking

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Hygiene				
Are you able to wash and dry your entire body?	_____	_____	_____	_____
Are you able to take a tub bath?	_____	_____	_____	_____
Are you able to get on and off the toilet?	_____	_____	_____	_____
Reach				
Are you able to reach and get down a 5 pound object (such as a bag of sugar) from just over your head?	_____	_____	_____	_____
Are you able to bend down and pick up clothing off the floor?	_____	_____	_____	_____
Grip				
Are you able to open car doors?	_____	_____	_____	_____
Are you able to open jars that have been previously opened?	_____	_____	_____	_____
Are you able to turn faucets on and off?	_____	_____	_____	_____
Activities				
Are you able to run errands and shop?	_____	_____	_____	_____
Are you able to get in and out of a car?	_____	_____	_____	_____
Are you able to do chores such as vacuuming or yard work?	_____	_____	_____	_____

Please check any AIDS or DEVICES that you usually use for these activities:

_____ Raised toilet seat

_____ Bathtub bar

- Bathtub seat
- Long-handled appliances for reach
- Long-handled appliances in the bathroom
- Jar opener (for jars previously opened)
- Other (specify: _____)

Please check any categories for which you usually need ASSISTANCE FROM ANOTHER PERSON

- Hygiene
- Gripping and opening things
- Reach
- Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK?

Place a mark on the line to indicate the severity of the pain.

No pain Very severe pain

IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?

Place a mark on the line to indicate the limitation of activity?

Do not limit activities Very severe limitation

IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?

Place a mark on the line to indicate the limitation of activity.

Do not limit activities Very severe limitation

IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?

Place a mark on the line to indicate the limitation of activity

Do not
limit activities


Very severe
limitation



IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities.
Place a mark on the line to indicate the limitation of activity.

Do not
limit activities

Very severe
limitation



Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?
Place a mark on the line to indicate the severity of your disease.

No disease

Very severe



Additional Comments: