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Therapeutic Plasma Exchange for the Treatment of Systemic Scleroderma: A Comprehensive Review and Analysis

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Abstract

Purpose. Systemic scleroderma (SSc) is a family of rare autoimmune disease that primarily affects middle age women. It is disabling, disfiguring, and steadily progressive, attacking internal organs through fibrotic processes in addition to its characteristic skin changes. Current treatment approaches focus on using immunosuppressants to slow the disease process plus interventions targeted at specific symptoms. Neither approach is currently very effective.

Therapeutic plasma exchange (TPE) has been tried as a treatment approach for SSc since 1978 based on the rationale that some circulating factor is involved in disease pathogenesis, e.g., autoantibodies or immune complexes, and that removing the potential pathogenic factors should lead to symptom improvement.

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 40 relevant articles that met our search criteria, involving a total of 533 patients. 15 of these were 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.

Conclusion. In contrast to current treatment modalities such as immunosuppression that carry significant risk and show limited efficacy, the results shown in the clinical studies reviewed for this article suggest that long-term TPE may offer a low-risk way to control and in some cases reverse SSc symptoms. The exact mechanism for the improvements seen from TPE in SSc patients is unclear. While most authors suggest that the benefits seen from TPE are primarily from the temporary reduction in potential circulating pathogenic factors, a number of authors have also noted that symptom improvements last significantly longer than would be expected if this was the sole mechanism of action, leading to the suggestion that improvements in blood rheology, such as

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increased RBC deformability and normalization of whole blood viscosity and RBC aggregation, may also be factors in the observed longevity of treatment effects.

Introduction

About Systemic Scleroderma

- Scleroderma (literally "hard skin") is an umbrella term for a family of rare diseases with the common factor being abnormal thickening (fibrosis) of the skin.
- While some variants of scleroderma are limited to skin changes and do not have internal organ involvement, the systemic forms of scleroderma are complex autoimmune diseases that can affect organs throughout the body, in addition to skin changes.
- Recent studies estimate that in the US the incidence of new cases of systemic scleroderma (SSc) is about 20 per million adults (about 4800 new cases per year based on current US population estimates) and that the current prevalence is about 240 cases per million adults (about 58,000 total active cases).
- SSc may occur at any age, but the symptoms most frequently begin in mid-life (25-45). SSc is very rare in children. The disease is about four times more common in women than men.
- About 90% to 95% of patients with SSc will test positive for antinuclear antibodies (ANA) when tested correctly using a method called indirect immunofluorescence or IFA. The different variants of SSc are primarily based on specific antibody type, with about eight different antibody-based variants. In addition, there is a small subset of patients that are ANA/antibody negative using current testing methods.
- SSc is grouped into three broad categories: “diffuse”, “limited”, and overlap syndromes. Diffuse and limited refer to the areas of potential skin involvement. Overlap syndromes have symptoms typically seen in other autoimmune diseases such as rheumatoid arthritis, lupus, and myositis in addition to typical scleroderma symptoms.

Shiny skin, peeling ulcer

Telangiectasias

Bent finger

Raynaud’s

Natural Course of Disease Progression

- Diffuse SSc (dcSSc) variants are characterized by rapid onset of symptoms, often beginning with severe pain and fatigue. With some patients, the disease progression may slow after the first couple of years. Patients with diffuse scleroderma variants may have significantly reduced survival, mostly due to lung, heart, and kidney involvement.
- Limited SSc (lcSSc) variants typically have a much slower progression rate than diffuse variants. The initial symptom is usually Raynaud’s for several years, followed by GI problems such as gastro esophageal reflux disease (GERD), difficulty swallowing, and

malabsorption. Patients with limited scleroderma variants often live near normal lifespans but with increasing disability and disfigurement over time.

- Overlap syndromes symptom development and progression rates vary based on specific antibody type but generally have a more favorable prognosis than patients with dcSSc.

Current Treatment Approaches

Systemic: Immunosuppression

- The majority of scleroderma researchers believe that autoantibodies may be involved in SSc pathogenesis. Because of this, the most common systemic treatment approach is to try to reduce overall or targeted immune system activity through the use of immunosuppressive drugs.
- Typical immunosuppressive drugs used (in order of increasing potential side effects) include hydroxychloroquine (Plaquenil), methotrexate (Trexall), mycophenolate mofetil (CellCept), and cyclophosphamide (Cytoxan), as well as targeted drugs such as rituximab (Rituxan).
- Research indicates that these drugs are not very effective for improving symptoms or slowing disease progression. The more toxic immunosuppressant drugs such as cyclophosphamide cannot be continued long-term because of potential harmful side effects that may cancel out any initial benefit seen during the treatment period.

Symptoms: Targeted

- Most treatments used in SSc focus on targeting specific symptoms. Examples include:
  - Raynaud's/digital ulcers: calcium channel blockers (e.g., nifedipine) or PDE5 inhibitors (sildenafil)
  - GERD: omeprazole
  - Gastroparesis: metoclopramide
  - Scleroderma renal crisis: ACE inhibitors

Therapeutic Plasma Exchange for Treating SSc

- Therapeutic plasma exchange (TPE) has been tried as a possible treatment for systemic scleroderma since 1978.
- The usual rationale and the primary post hoc explanation for any benefits seen from TPE is that TPE treatments temporarily reduce the levels of circulating factor(s) (e.g., autoantibodies or immune complexes, cytokines or adhesion molecules) that are presumed to be involved in SSc pathogenesis.

Method

- An initial Google Scholar search of all of the research literature was conducted using the following search terms:

  (plasmapheresis OR "plasma exchange" OR PEX OR TPE OR apheresis) AND (scleroderma OR "systemic sclerosis" OR PSS OR MCTD OR CREST OR Raynaud's)

- MCTD (Mixed Connective Tissue Disorder) was included as this is now considered a scleroderma overlap syndrome.
- Inclusion criteria: English abstract
- We obtained source copies of all articles identified during the search process and reviewed all references in these article to identify additional candidate articles. This process was repeated with all newly identified articles until no additional articles meeting our search criteria were found.

Results

Overview

- We identified 40 articles that met our search criteria, involving a total of 533 patients.
- 15 of the articles were case reports, involving a total of 21 patients. The remaining 25 articles (512 patients) ranged from letters to the editor describing a small group of patients treated with TPE to a large scale review of 102 patients treated over a 15-year period at a single clinic in Italy. All case reports are documented in Table 1. Observational studies and clinical trials are documented in Table 2.
- One significant issue in reviewing early case reports and studies was that prior to 1980 there were no formal classification criteria for diagnosing SSc. Prior to the adoption of formal Classification Criteria by the American College of Rheumatology in 1980, most studies used the term "secondary Raynaud's" to describe patients with autoimmune diseases typically characterized by Raynaud's symptoms. From descriptions of the patient's symptoms in most of the studies done before 1980, almost all patients were likely to have some sort of SSc. However, it should be noted that Raynaud's can also be a symptom of other autoimmune diseases such as lupus, potentially confounding interpretation of some of these early reports.
- As part of our review process, we have included a subjective grading system on the quality and completeness of the case reports, observational studies, and clinical trials. Unfortunately, only nine of the 40 studies reviewed for this report met our top grading criteria. Sixteen studies are missing some important information, but there is still useful information to be gleaned from these studies. The remaining 15 studies are either poorly designed, include limited or confusing information, or simultaneous multiple treatment interventions that make it impossible to determine if any reported symptom or laboratory measure improvements can be attributed to the TPE treatments.
- Table 1 below summarizes the findings of the key case reports and studies based on our detailed review of the literature. Detailed summaries of all case reports are shown in Table 2. Detailed summaries of clinical trials and observational studies are shown in Table 3.

Table 1: Key Case Reports, Clinical Trials, and Observational Studies

Study	Type*	Subjects	Treatments	Results
Ferri et al. 1992	CR	1) Female, 50, lcSSc, severe lung impairment	1) 3 TPE/week for 6 weeks, 2 TPE/week for 4 weeks, then 1 TPE/week for 2 weeks; Total TPE: 29/3 mo	1) major improvement in lung parameters, e.g., DLCO: 32% to 50%, FEV1: 89% to 103%, pO2: 67-99 mmHg
		2) Male, 59, lcSSc, severe lung	2) 3 TPE/week initially;	2) major improvement in

		involvement	maintenance 3 TPE/month; Total TPE: 25/4 mo	dyspnea, pO2: 40 to 67 mmHg and other symptoms; regressed after pneumonia; repeated cycle again with similar improvement; improvement maintained by maintenance TPE
Ferri et al. 2000	CR	Female, 22, U3-RNP positive dcSSc with severe PAH and diffuse skin changes	3 TPE/week for 2 months, slowly tapered to 3 TPE/month; Total TPE: ?/2 yrs	After 4 months, dyspnea, tachycardia, and systolic pulmonary arterial pressure (SPAP) returned to normal levels. TPE was discontinued after 2 years because of catheter related sepsis. Her SPAP remained stable for one year following discontinuation of TPE treatments.
Weiss et al. 2015	CR	Male, 46, lcSSc, severe GERD, Raynaud's, reduced DLCO/VA	1 TPE/week for 4 weeks, repeated every three months (16 treatments per year); Total TPE: >340/21 yrs	All symptoms except for mild Raynaud's resolved after 2-3 years. Patient has been in remission for 20 years with continued regular TPE treatments.
O'Reilly et al. 1979	RCT	n=27, secondary Raynaud's	Placebo (n=9), heparin (n=9), 1 TPE/week for 4 weeks (n=9)	Only TPE group showed improvements in symptoms and vascular patency; improvements maintained at 6 month follow up
Von Rhede van der Kloot et al. 1985	CT	n=14, 7 with primary Raynaud's, 7 with secondary Raynaud's	1 TPE/week for 4 weeks	Primary Raynaud's group: normal blood rheology, no benefit from TPE. Secondary Raynaud's group: viscosity and RBC aggregation elevated, significant benefit from TPE including healing of digital ulcers.
Weber et al. 1985	CT	n=36, 21 with primary Raynaud's, 15 with secondary Raynaud's	1 TPE/week for 4 weeks (only 9 patients received TPE, all in secondary Raynaud's group)	Essentially the same results as Von Rhede van der Kloot (85).
Jacobs et al. 1991	CT	n=18, SSc	1 TPE/week for 4 weeks; no other treatments	Measured changes in rheology and clinical symptoms; all patients improved; Raynaud's disappeared and skin ulcers healed; abnormal blood rheology normalized; Raynaud's returned in 14 patients in 6-9 months; RBC aggregation returned to baseline after 9 months; skin ulcers did not return in 3 year follow-up period.
Ding et al. 1985	CT	n=29	TPE plus D-penicillamine (n=13), control D-penicillamine only (n=16), 1 TPE per week for 6 weeks	Abstract only-article in Chinese. All parameters in TPE group showed significant improvement at end of treatment period; at 18 month follow up all parameters still

				significantly better than control group.
Cozzi et al. 2012	OS	n=20, SSc with renal crisis	ACE inhibitors plus varied TPE (n=10), ACE inhibitors only (n=10), protocol 2-3 TPE/week for first month, 1 TPE/2 weeks for maintenance	TPE group: 2/10 developed end stage renal disease (ESRD), 90% survival at 1 year, 70% survival at 5 years. Non-TPE group: 9/10 developed ESRD, 50% survival at 1 year, 30% survival at 5 years.

* CR: Case Report RCT: Randomized Clinical Trial CT: Clinical Trial OS: Observational Study

TPE and Healing of Digital Ulcers

One of the most striking and common findings reported in many of the studies reviewed for this article was that for the majority of patients Raynaud's symptoms usually disappeared completely or were significantly reduced and long-standing digital ulcers (DU) started healing after three to four TPE treatments. DU healing was mentioned in 14 of the 40 reviewed articles. The implications of this are discussed below.

Discussion

When Does TPE Fail to Work?

- Guillevin et al. (1983) tried TPE treatments in seven patients with severe dcSSc after failure of other treatments. In three patients, TPE treatments had to be stopped because of venous access problems. In the remaining four patients, only one showed benefit: improvement of articular and cutaneous symptoms. This suggests that TPE may not be effective in late stages of SSc.
- Capodicasa et al. (1983) tried TPE in two patients in scleroderma renal crisis (SRC). While brief improvement was seen in one patient, the authors concluded that TPE would need to be started earlier to be potentially effective. One complication with this study is that they used membrane TPE instead of centrifugal TPE. All other studies that we reviewed for this paper used centrifugal TPE. Also, ACE inhibitors are now used as the treatment of choice for treating SRC.
- While TPE was not effective in all patients in studies with overall positive outcomes, unfortunately, little data was presented about patients who failed to respond to TPE treatments. However, it was clear that most authors felt that TPE would be most effective if started early in the disease process.

Why Does TPE Show Positive Results?

Reduction of Potential Circulating Pathogenic Factors

The rationale for trying TPE has been based on the assumption that some circulating factor such as autoantibodies is involved in disease pathogenesis and that TPE will temporarily reduce any potential circulating pathogenic agent.

Abnormal Blood Rheology May Be Pathogenic in SSc

- Over the past 41 years, a number of published studies have consistently documented that blood rheology is abnormal in patients with systemic sclerosis (SSc). Individual studies have focused on differing aspects of this abnormal rheology including elevated

whole blood viscosity (WBV), plasma viscosity (PV), and abnormal red blood cell aggregation.

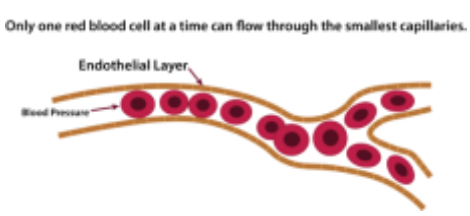
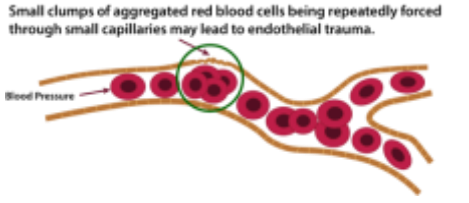
- The nature of the observed RBC aggregation is not discussed but does not appear to be referring to normal, easily reversible Rouleaux formation.
- While the significance of this abnormal rheology is not yet fully understood, the observation that TPE alone has a striking effect on clinical symptoms such as Raynaud's and digital ulcers and also leads to significant improvements in blood rheology suggests the presence of a plasma related pathogenic factor in SSc (Harris, Moriarty et al. 2016).
- Abnormal rheology in autoimmune diseases is not uncommon. It has been documented in rheumatoid arthritis (Gudmundsson et al. 1993) and systemic lupus erythematosus (Rosenson et al. 2001). However, TPE does not improve clinical symptoms in RA (Dwosh et al. 1983), suggesting a different mechanism of action in RA pathogenesis.
- Volkov et al. (2006) documented that patients with SSc have increased WBV relative compared to matched healthy controls, replicating many previous studies. In addition, they documented that WBV was highest in patients with active DU.

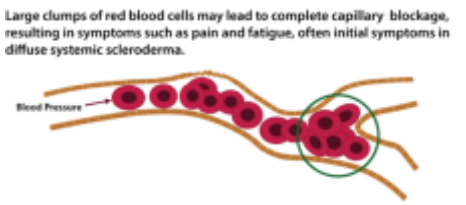
The Potential Role of RBC Aggregation in SSc Pathogenesis

- In 1979, Kahaleh et al. noted, "Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing."
- Hypothesis: abnormally clumped red blood cells may be a significant component of the etiopathogenic processes in SSc, potentially contributing to the vascular damage cited above. Possible endothelial damage mechanisms include biochemical processes or direct mechanical effects tending to re-model vessel walls and changes due to local ischemia caused by abnormal distribution of red cells in the microcirculation.

Support for RBC Aggregation Hypothesis

- The frequently reported finding that Raynaud's symptoms usually disappear and digital ulcers start to heal after three or four weekly TPE treatments is consistent with the idea that the microvascular damage seen in SSc is a direct result from aggregated red blood cells. Elimination of RBC aggregation would allow the vascular system to begin to heal due to increased blood flow.

Normal Blood Flow	
Endothelial Damage	

Microcapillary Blockage	

- McCune (1983), when comparing the effects of standard TPE with "sham" TPE that returned the patient's own separated blood instead of replacing the plasma with sterilized albumin, noted that improvements were seen in several objective measures and clinical symptoms in patients in both the normal treatment group and the "sham" treatment group. Since their "sham" treatment group did not reduce circulating antibody levels, the observed improvements in objective measures and clinical symptoms are likely to be a result of the RBC disaggregation effects that would have occurred in both treatment groups.

Issues/Concerns About the Use of TPE for Treating SSc

TPE Treatments are Required Indefinitely

- The beneficial effects from a single round of four weekly TPE treatments last three months or longer. Once TPE treatments are stopped, blood rheology gradually returns to pre-treatment levels and symptoms that improved during and following TPE treatments gradually return as well. Some treatment effects, for example healing of digital ulcers, appear to last for a much longer period of time - at least three years in the Jacobs et al. (1991) study.
- This suggests that TPE treatments will need to be continued on a permanent and regular basis in order to provide the maximum possible benefit. However, this is also true of any other current treatment approach with the possible exception of autologous stem cell transplants (HSCT). It should be noted that is not unusual with any chronic disease, e.g., the use of insulin to control/prevent diabetes symptoms and the use of antiretroviral drugs to prevent HIV complications.

Safety

- The safety profile for long-term use of TPE is excellent. The most common side effects are very short term, e.g., hypotension or fatigue for a few hours following a treatment.
- Cid et al. (2014) reviewed the efficacy and safety of TPE in 317 patients and 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 they were able to complete the scheduled TPE treatment.

Venous Access

- The best way to perform TPE is using regular peripheral venous access. Venous access problems were discussed in a number of the articles and were the reason for discontinuation in a number of instances.
- While the exact percentage of patients that would require alternative to standard peripheral venous access is not clear, the data suggest that the majority of patients can undergo long-term TPE using peripheral access. Khatri et al. (2013), summarizing the

results from more than 60,000 TPE treatments, indicates that peripheral venous access is successful in about 75% of the procedures performed at their clinic.

- 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 (Deguzman et al. 2012).
- While ultrasonic-guided peripheral venous cannulation requires special equipment, a recent study (Costantino et al. 2005) showed that this technique is more successful than traditional "blind" techniques, requires less time, decreases the number of percutaneous punctures, and improves patient satisfaction in the subgroup of patients who have difficult intravenous access.
- For patients who cannot undergo normal peripheral venous access, there are number of alternatives that are available. Central catheters are not a good option for most patients for long-term TPE because of the significant infection risk. 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 is not an option.
- While not generally used, Khatri (2013) reports successful use of temporary radial or brachial artery catheterization in more than 8000 procedures over a 30-year period.

Cost

- Winters (2011) did an analysis of TPE cost and determined that each treatment cost a little under $1200 when TPE was performed using albumin. 2015 average Medicare reimbursement rates are about $1140 plus the cost of albumin, which varies depending on the size of the patient.
- Several studies suggest that between 12 and 18 treatments per year may be sufficient to control SSc symptoms. Using the 16 TPE treatment per year protocol discussed in Weiss (2015), this works out to an annual cost of about $20,000 per year.
- A recent study of the annual cost of modern biologic drugs now commonly used to treat rheumatoid arthritis and other autoimmune conditions (Howe et al. 2014) 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.

Research and Treatment Implications

Research is Needed to Determine Validity of RBC Disaggregation Hypothesis

- It is important to determine: 1) if TPE is an effective treatment for some or all variants of SSc, and if so, 2) whether the beneficial effects from using TPE are from:
  - temporary reduction of potential blood circulating pathogenic factors such as autoantibodies,
  - disaggregation of aggregated red blood cells,

- or a combination of both.

Proposed initial clinical trial:

- Study should be restricted to anticentromere antibody (ACA) positive lcSSc patients within 5 years from diagnosis. Restricting the subject population to a slower-progressing variant of SSc with a single common antibody type would create a "best-case" study. If TPE is not effective in this population, it would be very unlikely to work in more rapidly progressing diffuse variants of SSc. Patients would also need to meet the Meet the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis (van den Hoogan et al. 2013).
- Study would be randomized, double-blinded, and placebo controlled with a non-treatment control group and two active treatment groups.
- One treatment group would receive standard TPE with plasma replacement by albumin 5%. The other treatment group would receive autologous TPE where the patient's plasma would be recirculated instead of being replaced by 5% albumin. (Note that is exactly what was noted as "sham pheresis" in McCune (83), where the researchers were surprised to see similar symptom improvement in several patients in both the regular and sham treatment groups.) It is possible to blind the patient by having the equipment visually screened so the patients could not observe whether or not they were part of the regular or autologous treatment group.
- Suggested protocol is the same as used in Weiss (2015): four weekly TPE treatments followed by two months with no treatments repeated four times per year for a total of 16 treatments during the first year. The length of the initial trial would need to be at least one year. This protocol was based on research that showed that four weekly TPE treatments completely disaggregates clumped RBCs and that this effect lasted at least three months.
- Suggested pre-treatment laboratory measures should include (at a minimum): pulmonary function test (PFT), ESR, CBC, circulating antibody levels, and whole blood viscosity. All measures except the PFT would be repeated ahead of and just after each round of four treatments. The PFT would be redone at the end of year one. Additional "softer" measures such as digital ulcers, frequency of Raynaud's attacks, and GI symptoms should be monitored as well. Note that in this particular patient population, skin changes may not be present in many of the patients so one common measure used in many of the reviewed studies. For this reason, the modified Rodnan skin score (mRSS) is not a suitable measure in this initial study.
- In addition to comparing the two treatment groups individually against the non-treatment control group, a comparison of the two treatment groups will provide important information about the relative contributions of temporary reduction in circulating pathogenic factors plus RBC disaggregation (as would occur in the regular TPE group) versus pure RBC disaggregation (as would occur in the autologous TPE group with no plasma replacement).

Proposed Initial Clinical Trial Results: Treatment Implications

There are three possible outcomes from the proposed clinical trial:

Neither Treatment Group is Significantly Better Than the Control Group

- This outcome would suggest that TPE is not likely to be an effective treatment for any variant of SSc. If TPE treatments are unable to lead to clinical improvements in

patients with slower progressing lcSSc, then it is very unlikely that they would lead to clinical improvements in more rapidly progressing diffuse variants of SSc.

Only the Standard TPE Treatment Group is Significantly Better Than the Control Group

- This outcome would suggest that while there may be some contribution from RBC disaggregation to the overall TPE treatment effects, the primary reason for any observed benefit is likely to be that TPE works by temporarily reducing circulating pathogenic factors such as autoantibodies – the original rationale and post-hoc explanation usually given for the positive outcomes described above.
- This outcome would still demonstrate that TPE may be an appropriate treatment for patients with ACA positive lcSSc and would justify follow-up research with patients with other common antibodies, such as Scl-70 and RNA Polymerase III, both of which are associated with dcSSc variants.

Both TPE Treatment Groups Are Significantly Better Than the Control Group

- This would be the most interesting potential outcome of the proposed initial clinical trial. If autologous TPE has any beneficial effects at all, these can *only* be from a direct biomechanical process such as direct RBC disaggregation since autologous TPE does not reduce the blood circulating levels of autoantibodies or other possible pathogenicfactors.
- This outcome would also raise the possibility that ANY treatment that can disaggregate clumped red blood cells or can prevent red blood cells from re-aggregating following initial TPE treatments may be an effective treatment option for SSc. As shown in many of the reviewed studies, TPE is one way of reducing RBC aggregation, but there may be potential pharmaceutical interventions as well that may have similar effects. (While beyond the scope of this paper, we have identified two possible drugs that may have potential to disaggregate clumped red blood cells or reduce the likelihood of future RBC aggregation following an initial round of TPE treatments.)
- Depending on the difference in treatment efficacy between the two treatment groups (if any), it may be possible to use autologous TPE instead of regular TPE as a treatment option, thus reducing cost by a significant amount since replacement albumin would not be required.

Summary and Conclusion

- The preponderance of evidence suggests that long-term TPE may offer a low-risk way to control and in some cases reverse SSc symptoms. In contrast to current immunosuppressive treatments that carry significant risk, long-term TPE appears to be safe, well tolerated, and with very few, mostly minor side effects. While TPE is a fairly expensive procedure, annual costs are in line with modern pharmaceuticals commonly used to treat SSc and other autoimmune diseases.
- The exact mechanism for the improvements seen from TPE in SSc patients is unclear. An initial clinical trial is needed to determine the relative contributions of temporary reduction in possible circulating pathogenic factors and direct RBC disaggregation to the overall TPE treatment effects.
- If research demonstrates that RBC disaggregation is the primary mechanism for the clinical improvements seen from TPE, this would suggest that ANY treatment that can

disaggregate clumped red blood cells and keep them from re-aggregating may be an effective treatment option for SSc, including pharmaceutical interventions as well as mechanical disaggregation through TPE.

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Table 2: Case Reports

Case Report	Patient / Diagnosis	Treatment	Duration	Results/Notes	Grade*
Kamanabroo et al. 1980	Female, 37, MCTD, painful swollen fingers, Raynaud's, polyarthritis, Sjogren's, severe leg ulcerations, bedridden	2 TPE/week initially, switched to 2 TPE/6 to 8 weeks	Not specified	Marked clinical improvement in 3 weeks, ulcers improved with tendency to regression, able to walk unaided	II
Hertman et al. 1981	Female, 12, MCTD, Raynaud's plus diffuse swelling of distal extremities, fingertips cyanotic, multiple abnormal labs	2 TPE/week initially, q3w maintenance	Not specified	Became asymptomatic with normal lab values	II
Gouet et al. 1982	3 patients, type II scleroderma (non-truncal skin involvement)	TPE plus immunosuppressives	Not specified	Loosening of skin, lessening of joint pain, resolution of weakness, decreased Raynauds. Article in French. In process of obtaining translation of full article.	III
Cadodicasa et al. 1983	1) Female, 42, dcSSc, in renal failure 2) Female, 38, lcSSc, progressive uremia	1) 3-4 TPE/ week plus hemodialysis 2) 1 TPE/ week	1) 2 weeks 2) 2 weeks	1) Transient improvement only 2) Decrease in skin and joint pain, smoothening of skin, improvement in swallowing. Note: membrane TPE.	II
Llewelyn et al. 1989	Female, 59, lcSSc, digital ulcers, swollen fingers with tight skin, calcinosis	2 TPE/ week initially, 1 TPE/month maintenance	Unclear	2 weeks after commencing TPE treatments, reduced Raynaud's attacks and healing of digital ulcers. Finger tightening occured just before each monthly maintenance TPE, reversing this symptom.	II
Ferri et al. 1992	1) Female, 50, lcSSc, severe lung impairment 2) Male, 59, lcSSc, severe lung involvement	1) 3 TPE/week for 6 weeks, 2 TPE/week for 4 weeks, then 1 TPE/week for 2 weeks 2) 3 TPE/week initially; maintenance 3 TPE/month	1) 3 months (29 total) 2) 4 weeks (12 total); 2 months off; 4 weeks (13 total)	1) major improvement in lung parameters, e.g., DLCO: 32% to 50%, FEV1: 89% to 103%, pO2: 67-99 mmHg 2) major improvement in dyspnea, pO2: 40 to 67 mmHg and other symptoms; regressed after pneumonia; repeated cycle again with similar improvement; improvement maintained by maintenance TPE	I
Tamura et al. 1992	Female, 47, interstitial pneumonia, digital ulcer, facial swelling, very elevated ESR, unresponsive to prednisone and cyclophosphamide	1 TPE treatment/day	3 days	Improvements in finger stiffness, dyspnea, chest x-ray. ESR dropped dramatically from 37 to 11 and was sustained at 3 month follow-up with no further TPE treatments.	II

Case Report	Patient / Diagnosis	Treatment	Duration	Results/Notes	Grade*
Van den Hoogen et al. 1993	Female, 50, dcSSc, Scl-70	2 to 3 TPE/week	29 days (11 total)	No changes seen in patient during study period, focus was on changes IgG antibody levels. These were slightly reduced briefly after each treatment (20% total reduction after 11 treatments) but returned to pre-treatment levels after 5 weeks post treatment.	II
Ferri et al. 2000	Female, 22, U3-RNP positive dcSSc with severe PAH, digital ulcers, diffuse skin changes, telangiectasias	3 TPE/week for 2 months, slowly tapered to 3 TPE/month	2 years	After 4 months, dyspnea, tachycardia, and systolic pulmonary arterial pressure (SPAP)returned to normal levels. TPE was discontinued after 2 years because of catheter related sepsis. However, her SPAP remained stable for one year following discontinuation of TPE treatments.	I
Seguchi et al. 2000	Female, 24, MCTD with multiple organ failures including renal failure.	2 TPE total plus immunosuppressants	Unclear	Raynaud's reduced immediately following 2 TPE treatments. Difficult to analyze because of multiple interventions.	III
Szucs et al. 2003	4 patients, rapidly progressing dcSSc, within 1 year of onset.	1 TPE/3 months	Unclear	Progression slowed down, no new clinical symptoms, improved skin scores. As dcSSc often improves spontaneously after the first year, at this low a TPE frequency it is very unlikely the improvements are from the TPE treatments. Article in Hungarian.	III
Szekanecz et al. 2009	Male, dcSSc, widespread skin involvement, digital ulcers, unresponsive to cyclophosphamide	3 TPE treatments every 2-3 months for a total of 15 treatments per year plus monthly IVIG	11 years	No clinical progression during the 11 year treatment period. The simultaneous use of IVIG and TPE does not allow determining if the results were from the IVIG, TPE, or combination.	III
Szodoray et al. 2014	Female, 53, MCTD plus antiphospholipid syndrome, severe ulcers on hands and feet	3-4 TPE treatments, repeated 3 and 6 weeks later plus cyclophosphamide combined with several other drugs	6 weeks	Improvement in digital gangrenes and no new lesions. However, too many interventions to separate out which interventions lead to symptom improvements.	III
Owlia 2015	Female, 39, probable dcSSc, puffy and shiny face, reduced oral aperture, abnormal nailbed, esophageal dysfunction	1 TPE/day	15 days	Modified Rodnan Skin Score dropped from 36 baseline to 18 after 3 weeks, dramatic improvement in skin stiffness, tendon rub, and Raynaud's after 3 treatments.	II
Weiss et al. 2015	Male, 46, anticentromere positive lcSSc, severe GERD, Raynaud's, reduced DLCO/VA, chronic chilling	1 TPE/week for 4 weeks, repeated every three months (16 treatments per year). No other systemic interventions.	21 years	All symptoms except for mild Raynaud's resolved after 2-3 years and patient has been in remission for 20 years with regular continued TPE treatments at the original treatment protocol frequency.	I

* Grade: I - Clear diagnosis, description of protocol, time period. No confounding with other treatments.
II - Clear diagnosis and description of protocol. No confounding with other treatments.
III - Protocol or time period not clear, multiple treatments used, other major issues.

Table 3: Clinical Trials and Observational Studies

Study	Description†	Participants	Treatment	Results/Notes	Grade†
Talpos et al. 1978	CT, brief report	n=5, severe secondary Raynaud's, 4 with severe digital ulceration	Five weekly TPE treatments	All ulcers but 1 healed, significantly reduced frequency of Raynaud's. In three patients, blood viscosity was measured and significantly improved. Symptom improvements lasted at least 6 months	II
Cotton 1978	CT, letter	n=12, 8 with secondary Raynaud's, 4 other	Varied	Improvement in 10/12 patients. 1 patient with severe gangrene completely reversed after 6 TPE treatments.	III
Dodds et al. 1979	CT	n=8, secondary Raynaud's,	1 TPE/week for 4 weeks	Focus was on changes in hemorheology; all patients reported symptom improvement including healing of digital ulcers; blood hyperviscosity significantly reduced after TPE treatments, persisted at 6 week follow up	II
O'Reilly et al. 1979	RCT	n=27, secondary Raynaud's	Placebo (n=9), heparin (n=9), 1 TPE/week for 4 weeks (n=9)	Only TPE group showed improvements in symptoms and vascular patency; improvements maintained at 6 month follow up	I
Hamilton et al 1980	CT	n=17, secondary Raynaud's	1 TPE/week for 4 weeks	Focus was on changes in circulatory improvement; all patients showed clinical improvement; whole blood viscosity was significantly reduced and maintained at 3 month follow up	II
Zahavi et al. 1980	CT	n=9, severe secondary Raynaud's	1 TPE/week for 4 weeks	Study focus was on platelet aggregation; the TPE group was a subset of a larger group; all patients in treatment group showed significantly improved arterial patency; clinical improvement noted in 7 patients including healing of digital ulcers	II
Dau et al. 1981	CT	n=15, SSc	1 TPE/week for up to 10 weeks, variable after; also used prednisone and cyclophosphamide	Improvements seen in 14/15 patients including healing of digital ulcers and skin changes. However, the protocol used does not allow differential determination of TPE effects versus immunosuppressive effects.	III
Guillevin et al. 1983	CT	n=7, late stage dcSSc	Variable, 8 to 20 TPE combined with prednisone in 5 patients	3 patients could not undergo TPE because of venous access problems; only one patient showed improvement but was also on prednisone; results suggest TPE not very effective in late stages of dcSSc	III
McCune et al. 1983	CT, included placebo TPE	n=6, mixed lcSSc and dcSSc	Treated with TPE, PPE, or both; 1 tx/week for four week; placebo TPE did not replace extracted plasma with albumin	Design was complicated but key finding here is that both regular TPE and "so called" placebo TPE worked with a number of patients, including improvements in blood viscosity.	II

Study	Description†	Participants	Treatment	Results/Notes	Grade†
Von Rhede van der Kloot et al. 1985	CT	n=14, 7 with primary Raynaud's, 7 with secondary Raynaud's	1 TPE/week for 4 weeks	This study demonstrated that blood viscosity and RBC aggregation is elevated in patients with secondary Raynaud's but not primary Raynaud's and that only patients with secondary Raynaud's benefit from TPE, showing reduced RBC aggregation; these patients also had reduced Raynaud's and some digital ulcer healing.	I
Weber et al. 1985	CT	n=36, 21 with primary Raynaud's, 15 with secondary Raynaud's	1 TPE/week for 4 weeks (only 9 patients received TPE, all in secondary Raynaud's group)	Patients with primary Raynaud's had normal blood rheology and did not benefit from TPE; patients with secondary Raynaud's had grossly abnormal blood rheology including RBC aggregation; 7 of 9 treated patients had major improvement in Raynaud's, healing of digital ulcers, and return of normal blood rheology.	I
Weiner et al. 1986	RCT, preliminary report	n=16, SSc 1 to 4 years duration	3 groups: placebo (n=5), TPE (n=5), lymphoplasmapheresis (n=6), 21 TPE/LPP treatments over 3 month period	Both TPE and LPP groups showed significant clinical improvements versus control group; LPP group showed better skin improvements than TPE group	II
Ferri et al. 1987	CT	n=6, dcSSc (n=5), lcSSc (n=1)	3 TPE/week for 3-4 weeks, slowly tapered, varied from 6 to 14 treatments over 5 to 37 weeks	1 patient dropped out because of venous access problems; significant but transient improvements including healing of digital ulcers during treatment period; no improvement in cardiovascular symptoms	II
Mascaro et al. 1987	CT	n=10, SSc, poor response to previous therapy	2 TPE/week for 4-6 weeks, 2-3 times per year, duration 6 months to 4 years	Significant improvement in 8/10 patients including complete or partial elimination of Raynaud's, healing of digital ulcers in 3/4 patients, skin improvement in 8/10 patients	II
Pourrat et al. 1987	CT	n=8, severe SSc	Variable, combined with immunosuppressants in some cases	Raynaud's improved in all patients; significant improvements of other symptoms including lung functioning and healing of digital ulcers; added immunosuppressants stopped with no detrimental effects in several cases.	III
Akesson et al. 1988	CT	n=15, severe dcSSc (n=12), lcSSc (n=3)	7 immunosuppressants only, 8 added TPE, protocol frequently changed	Poorly designed study; impossible to extract useful information	III
Schmidt et al. 1988	CT	n=19, SSc	Initially 3 TPE/week, then weekly, bi-monthly, and monthly for 12 to 18 months	Abstract only – article in French. Positive and lasting results in 11 patients, 2 stable, 3 worsening; 3 stopped because of venous access issues. Difficult to assess clinical changes.	III
Guillevin et al. 1990	OS	n=40, variable SSc and symptom profile	TPE done either by centrifuge or filtration, 1 to 110 treatments, average 6 months and 30 treatments, often combined with immunosuppressants	Overall TPE effective in 52% during treatment period and three month follow up; benefits did not persist for long period after cessation of TPE; study has too many variables to be useful other than to note that TPE has to be continued to see long-term benefit	III

Study	Description†	Participants	Treatment	Results/Notes	Grade†
Jacobs et al. 1991	CT	n=18, SSc	1 TPE/week for 4 weeks; no other treatments	Measured changes in rheology and clinical symptoms; all patients improved; Raynaud's disappeared and skin ulcers healed; abnormal blood rheology normalized; Raynaud's returned in 14 patients in 6-9 months; RBC aggregation returned to baseline after 9 months; skin ulcers did not return in 3 year follow-up period.	I
Vlasenko et al. 1992	CT	n=12, varied SSc non responsive to previous treatments	Combined TPE and lymphocytoplasmapheresis 3-5 times at 2-3 day intervals	Abstract only-article in Russian; protocol information very unclear; short-term benefit but no follow up information.	III
Dau et al. 1994	CT	n=8, dcSSc	Combination of TPE (weekly) IVIG, prednisone, and cyclophosphamide	Focus on immunological markers; complex combined protocols prevent any useful interpretation of possible TPE effects	III
Ding et al. 1995	CT	n=29	TPE plus D-penicillamine (n=13), control D-penicillamine only (n=16), 1 TPE per week for 6 weeks	Abstract only-article in Chinese. All parameters in TPE group showed significant improvement at end of treatment period; at 18 month follow up all parameters still significantly better than control group.	I
Cozzi et al. 2001	CT	n=53, dcSSc (n=32), lcSSc (n=21)	28 in treatment group, 25 in control group; treatment group received long-term TPE (2-3/week for 2 weeks, weekly for 3 months, bi-weekly for maintenance, mean 33 months) plus D-penicillamine, control group D-penicillamine only	Many flaws in this study; treatment group significantly worse than control group pre-treatment; however, only the treatment group showed improvements in laboratory markers and clinical scores.	II
Marson et al. 2001	OS	n=102 over 15 year period	Varied	Overall, the majority of patients showed symptom improvements and reduction of laboratory disease markers; overall safety profile of 7,557 TPE treatments was excellent (only 3 serious problems); TPE was not effective in several patients with scleroderma renal crisis	II
Cozzi et al. 2012	OS	n=20, SSc with renal crisis	ACE inhibitors plus varied TPE (n=10), ACE inhibitors only (n=10), protocol 2-3 TPE/week for first month, 1 TPE/2 weeks for maintenance	TPE group: 2/10 developed end stage renal disease (ESRD), 90% survival at 1 year, 70% survival at 5 years, non-TPE group: 9/10 developed ESRD, 50% survival at 1 year, 30% survival at 5 years.	I

* CT: Clinical Trial RCT: Randomized Clinical Trial OS: Observational Study

† Grade: I - Effectiveness of TPE treatments can be clearly determined.
II - Clear trend suggesting that TPE treatments are beneficial, but problems with study design or incomplete information.
III - Poorly designed study, limited information, or multiple treatments applied making it impossible to determine effects of TPE treatments.