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

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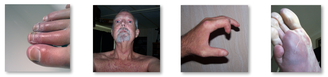
Introduction

- Systemic Scleroderma (SSc) is an umbrella term for a family of rare diseases with the common factor being abnormal thickening (fibrosis) of the skin. SSc is a complex autoimmune disease that affects internal organs as well as the skin.
- Estimated incidence (US): 20/million (4800/year new cases), prevalence: 240/million (58,000 diagnosed 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 4 times more common in women than men.
- SSc is divided into two general categories: diffuse (dcSSc) and limited (lcSSc). dcSSc patients usually have rapid onset of symptoms and significantly reduced survival, mostly due to lung, heart, and kidney involvement. lcSSc patients have a slower onset and progression rate, often live near normal lifespans but with steadily increasing disability and disfigurement over time.
- 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 for SSc since 1978 but has not been widely used or studied.



Method

- An initial Google Scholar search was conducted using the following search term: *(plasmapheresis OR "plasma exchange" OR PEX OR TPE OR apheresis) AND (scleroderma OR "systemic sclerosis" OR PSS OR MCTD OR CREST OR Raynaud's)*. 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.
- Fifteen 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.
- Our review process included a subjective grading system on the quality and completeness of the articles. Nine articles met our top grading criteria. Sixteen studies were flawed but provided useful data. The remaining 15 studies had major flaws that made it difficult to fully determine the efficacy of TPE.
- Table 1 includes a summary of the top 9 reviewed articles.

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 started healing after 3 to 4 TPE treatments. This was mentioned in 13 of the 40 reviewed articles.

Table 1: Key Case Reports and 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 involvement	2) 3 TPE/week initially; maintenance 3 TPE/month; Total TPE: 25/4 mo	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
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. 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.
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 CT: Clinical Trial RCT: Randomized Clinical Trial OS: Observational Study

Discussion

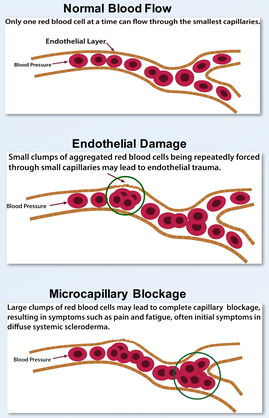
The standard explanation for any beneficial effects from TPE is that it temporarily reduces the circulating levels of some pathogenic agent such as autoantibodies.

Alternative Hypothesis – RBC Disaggregation Model

- A series of studies published between 1975 and 2008 have consistently shown abnormally elevated blood viscosity in the majority of systemic scleroderma patients. The overall elevated blood viscosity is a direct result of abnormally aggregated red blood cells.
- In 1979, Kahaleh et al. noted that "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: aggregated red blood cells that are forced though capillaries that are small enough so they normally permit passage of one red blood cell at a time may lead to the vascular damage cited above as well as potential microcapillary blockage. Possible endothelial damage mechanisms include 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

- In 1991, Jacobs et al. documented that a single series of four weekly TPE treatments significantly reduced RBC aggregation and plasma viscosity ($p<.001$) for about 9 months and eliminated Raynaud's symptoms for 6 to 9 months in all subjects. Dodds et al. (1979) and others have also documented increased RBC deformability following TPE treatments.
- The frequently reported finding that Raynaud's symptoms usually disappear and digital ulcers start to heal after 3 or 4 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.
- McCune (1983), when comparing the effects of standard TPE with "placebo" 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 in both treatment groups. Since their "placebo" group did not reduce circulating antibody levels, these benefits are likely to be from the disaggregation effects which would have occurred in both groups.



Long-Term TPE: Issues/Concerns

TPE Treatments are Required Indefinitely

The beneficial effects from a single round of 4 weekly TPE treatments last at least 3 months. Once treatments are stopped, blood rheology and symptoms gradually return to pre-treatment levels. This indicates that TPE treatments need to be continued on a permanent basis in order to provide the maximum possible benefit (e.g., Weiss et al. 2015). However, this is also true of any other current treatment approach.

Safety

The safety profile for long-term use of TPE is excellent. The most common side effects are very short term, for example hypotension or fatigue for a few hours following a treatment. An 11-year review of the safety of TPE in 317 patients and 2730 procedures (Cid et al. 2014) showed an adverse event rate of 3%, all of which were mild.

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 was the reason for discontinuation in a number of instances.
- There is a significant infection risk with central catheters for long-term TPE. Alternatives such as fistulas or newer ports such as Vortex™ may be better options for very-long term use of TPE if peripheral venous access is not an option. While rarely 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. This is comparable to Medicare reimbursement rates for TPE treatments.
- Several studies suggest that between 12 and 18 treatments/year may be sufficient to control SSc symptoms. Using the 16 TPE treatment/year protocol discussed in Weiss (2015), this works out to an annual cost of about $20,000 per year.
- Modern biologics commonly used to treat rheumatoid arthritis and other autoimmune condition cost between $21,000 and $24,000 per year (Howe et al. 2014). 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 if: 1) 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 in circulating pathogenic factors, disaggregation of red blood cells, or a combination of both.

Proposed Initial Clinical Trial

- Randomized, double-blinded, placebo controlled trial of anticentromere antibody (ACA) positive lcSSc patients within 10 years from initial symptoms.
- Two active treatment groups: 1) standard TPE; 2) autologous TPE (patient's plasma recirculated instead of being replaced). Use Weiss et al. (2015) protocol: 4 weekly TPE treatments, 2 months' rest, repeat (16 treatments/year). Duration: 1 year.
- Lab measures – baseline: pulmonary function test (PFT), ESR, CBC, ACA level, whole blood viscosity. All measures except PFT repeated before/after each treatment round. Other measures: Raynaud's attacks, digital ulcers, GI symptoms.

Outcome Interpretation

- *Neither Treatment Group is Significantly Better Than the Control Group*: TPE is not likely to be an effective treatment for any variant of SSc.
- *Only the Standard TPE Treatment Group is Significantly Better Than the Control Group*: 1) TPE is an effective treatment of ACA-positive lcSSc patients; and 2) TPE effects are mostly from temporary reduction of circulating pathogenic factors.
- *Both TPE Treatment Groups Are Significantly Better Than the Control Group*: 1) TPE is an effective treatment of ACA-positive lcSSc patients; and 2) TPE effects are primarily from RBC disaggregation.

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 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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