Scleroderma as a Hyperviscosity Syndrome
Implications for Treatment and Research

Background

According to a number of research studies, scleroderma is a hyperviscosity syndrome. Basically, in lay terms, viscosity is a measure of the “thickness” of a fluid. For example, water has a much lower viscosity than honey. The earliest study was done in 1977, and a number of studies again showing this (as well as looking at a potential way to treat this) were done in the Netherlands in the 80s. More recently, about five years ago this finding was replicated using a new technology to measure blood viscosity (more on this later). What this means is that in scleroderma, blood is overall “thicker” than it normally is when compared to the normal population. Specifically, the red blood cells are clumping together in a way that makes the overall blood too thick.

So why is this relevant? Consider the following: the average diameter of a red blood cell is 6 to 8 µm. The diameter of a micro-capillary is as small as 5 µm, about 25% smaller than the red blood cell. This means that red blood cells fold to fit through the smallest capillaries. As red blood cells start to clump together, it becomes increasingly difficult for the “clump” of red blood cells to make it through the smallest micro-capillaries. However, blood pressure is very strong, and at least for a while, the pressure will be strong enough to force the clump through the micro-capillaries. However, at some point, this will start to cause damage to the cells that line the micro-capillaries. When you search the research literature on the effects of hyperviscosity on micro-capillaries, you quickly find articles that document most of the early symptoms seen in SD, including tortuous capillaries that are seen in nail beds and glomerular damage (kidneys) caused by hemodynamic mechanisms.

One obvious question that has not been researched, to the best of my knowledge, is whether there is a different degree or type of hyperviscosity in limited vs diffuse SD. Diffuse SD progresses more rapidly, and differently, than limited SD. Is this because there is greater hyperviscosity in diffuse SD? Determining if there is a different degree/type of hyperviscosity between ACA positive limited SD patients anti-SCL 70 positive diffuse patients is a research study that clearly should be done, in my view.

Treatment Implications

When I first learned in early 1993 that SD appeared to be a hyperviscosity syndrome, I found a series of research articles, mostly done in the Netherlands, that looked at hyperviscosity in primary vs secondary Raynauds. Primary Raynauds is not related to SD and occurs mostly in younger female patients and is actually fairly common. Secondary Raynauds is what we deal with as part of SD. What the
research showed was that with Raynauds secondary to SD, the red blood cells were highly aggregated (clumped), however with primary Raynauds they were not although overall blood viscosity was slightly elevated even in primary Raynauds patients. While this information is clearly significant, what is more significant is what the research group also did to alter the blood hyperviscosity.

Basically, the researchers used a treatment called plasmapheresis on both primary and secondary Raynaud’s patients. Basically, what plasmapheresis does is to mechanically replace most of the plasma while preserving the red and white blood cells. Specifically, the procedure involved removing blood from one arm, running it through a machine that centrifuges out and keeps the red and white blood cells, discards the plasma (the liquid part of the blood), and replaces it with either new plasma or more commonly sterilized albumin. The combined albumin and the original red and white cells are remixed and returned to the other arm. Typically this takes about 1 ½ hours and is done in an outpatient hospital environment. The effect of a plasmapheresis treatment is to basically remove about 80 to 85% of everything in the blood except the red and white blood cells. This includes beneficial things like clotting factors but also potentially harmful things such as antibodies.

The treatment protocol in these early studies mostly involved doing four plasmapheresis treatments – one per week for four weeks – and then studying the results of this intervention. What they found was that it had little effect on primary Raynauds (non-SD) patients, but typically eliminated the Raynaud’s symptoms in SD patients for a number of months before returning.

When I first discovered this research in 1993, it changed my view of how to think about possible ways to treat SD. The research suggested to me that regardless of the cause of the disease, the initial clinical manifestation is hyperaggregation of the red blood cells, presumably resulting from the presence of the specific antibodies we see in SD. My hypothesis at that time was that the hydraulic pressure forcing clumps of red blood cells through the micro capillaries causes damage to the cell walls, eventually leading to the cluster of symptoms we call scleroderma.

If this hypothesis is correct, this would suggest that there are fundamentally two ways to deal with the disease:

(1) develop a treatment that elements whatever is producing these antibodies in the first place, or

(2) eliminate as many of the antibodies themselves from the blood with the hope that this will at least delay or stop progression of symptoms.
The first approach potentially cures SD and should result in ANA levels returning to normal. However, given that there appear to be multiple triggers for scleroderma, as well as different forms of the disease, this will not be easy to achieve. (It is worth noting, however, with some anecdotal reports of patients that respond to antibiotic therapy, their antibody levels typically do return to normal levels. Assuming that a subset of scleroderma patients have their disease triggered by an infectious process, e.g., mycoplasma, eliminating the infection would reasonably be expected to eliminate the destructive antibodies, resulting in ANA levels returning to normal.)

The second approach is based on the disease model that suggests that SD progression occurs because of damage caused by the red blood cell hyperviscosity, regardless of the ultimate cause of SD. It is analogous to treating diabetes with insulin or using antiretroviral treatments to prevent HIV infections from ever developing into AIDS. Insulin does not cure diabetes but if carefully monitored and used correctly, symptoms develop much more slowly than for untreated diabetics. Similarly, antiretroviral treatments to not deal with the underlying HIV infection, but if started early enough and used diligently, patients with HIV can lead essentially normal lives. Note that this second treatment approach would be unlikely to reduce ANA levels in scleroderma since the antibodies are still being generated, but their destructive impact would be greatly reduced or eliminated.

As an important side note, when I did this initial investigation almost 20 years ago, there was very limited research on using plasmapheresis for treating hyperviscosity syndromes. Nowadays, if you do a Google search for treatment of hyperviscosity syndromes, plasmapheresis is universally listed as the preferred and often only treatment option. The fact that Scleroderma is also a hyperviscosity syndrome is not yet well known (I plan on updating the Wikipedia article on hyperviscosity syndromes in the near future).

So the obvious question is: does this approach—using plasmapheresis as a way of preventing or slowing down the progression of the SD—work? The short answer is yes, in some cases, based on one anecdotal report of a patient that has been undergoing regular plasmapheresis treatments for more than 19 years at this point (me).

Here is more information about this treatment approach that you should be aware of:

1) Because this treatment approach works by preventing progression of symptoms rather than curing the underlying disease, it needs to be continued regularly and indefinitely to be an effective control. If the treatment is stopped, the disease symptoms will return after a while and continue progressing again. (I tried this once—not by choice—and symptoms began to return about 6 months later. I took a
full year of my standard treatment regimen to eliminate all symptoms again.)

If people get nothing else out of this document, I think this may be one of the key things for patients interested in trying plasmapheresis to understand. I occasionally run into reports where a SD patient will say something like “I tried plasmapheresis treatments a few times some years ago. It seemed to help for a while but then symptoms returned so we decided to try xxx again...”. If you paraphrase this as “I have diabetes and we tried insulin a few times. I seemed to help but my symptoms returned so we decided to try something else”, you can easily see why this is exactly what you would expect if you stop regular plasmapheresis treatments, allowing the blood hyperviscosity to re-occur with the resulting return of systemic damage.

2) Based on discussions with the researchers who first started using this in the Netherlands in the late 80s, a recommended treatment cycle for a patient with limited SD (CREST) is one treatment a week for four weeks, wait two months, and repeat for a total of 16 treatments per year. This is my current treatment cycle. I tried stretching this out gradually about 8 years ago, but when the treatment gap approached 3 months instead of the normal 2 months, symptoms began to return so I returned to the baseline 16 treatment per year model. I suspect that this may vary with different people.

3) The researchers actually tried this with diffuse patients. In contrast with treating limited SD patients with 16 treatments per year, they found that if they did plasmapheresis weekly, they could stop progression in diffuse patients. However, after about 1 ½ years, the patient’s immune system started to break down and they began to develop other problems as a result that prevented continuing weekly treatments. They guessed that a less frequent regimen would slow the progression with diffuse patients but not stop it entirely but had not tried it. It is also possible that with modern plasmapheresis technology, this might be less of an issue, but there is no data to suggest this either way so this would be just speculation pending actual research.

4) If treatments are started early enough before major systemic damage has occurred, plasmapheresis treatments can allow the body to heal to some extent. In my case, when I started I had severe reflux, some early stage loss of lung functioning, heart irregularities, etc. (no skin changes). After two years of regular treatments, all of these problems disappeared and my lung functioning returned to the normal range. If treatments are started later, it is likely that some damage will not be reversible but disease progression may be halted. It is also possible some improvement may well be seen in body parts where cells regenerate more rapidly, e.g., skin and GI tract, even at later disease stages.

**Cost and Insurance Coverage Issues**
One of the reasons I have waited until now to make more people aware of this treatment option is that it is costly and can realistically be done only if insurance covers it. It was very surprising that my insurance company agreed to initially do a one year trial 19 years ago (there is a reason for this which I can explain if anyone is interested). When it clearly was working after one year, they continued covering it and did so until I just turned 65 this August – more than 18 years in total. I was very concerned that Medicare would not cover plasmapheresis treatments for scleroderma, at least without going through the appeals process. However, it turned out that they did cover the treatments routinely. I eventually was able to track down the Medicare guidelines for use of plasmapheresis. Plasmapheresis is now listed as a covered treatment for “… life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy”. The fact that they covered my treatments immediately is certainly encouraging. Most insurance companies will cover anything that Medicare covers but it might take some time and effort to get some insurance companies to be willing to consider this approach to treating scleroderma.

However, even if insurance companies may be willing to cover plasmapheresis treatments for controlling scleroderma, access can still be a problem, especially in rural settings. Any large hospital is likely to have the necessary equipment to do plasmapheresis treatments on an outpatient basis. In a smaller community, plasmapheresis treatments may be not be as readily available. On the other hand, if the number of treatments is limited as indicated in this article, in some cases, traveling some distance to a larger hospital for infrequent treatments may still be feasible.

**Research Possibilities**

I mentioned earlier that a few years ago a company developed a new technology for doing hyperviscosity testing. There is a lab (Meridian Valley Lab) that does blood viscosity testing using this new system (Hemathix SCV-200). I am actually in contact with the CEO of the company that makes this equipment and it is possible that they might be willing to discount the test costs for research studies (not sure about this).

With the ready availability of blood viscosity testing, there are a lot of obvious studies that should be done, for example, looking at blood hyperviscosity in limited vs diffuse SD. But at a minimum, it seems that any general treatment study for SD should include blood hyperviscosity testing as a dependent measure. Is it possible that the reason that some of the drugs used to treat SD have some beneficial effect because they are reducing the hyperaggregation of the red blood cells?
Also, does this mean that it might be possible to develop a drug that targets the red blood cell clumping specifically as a way to control the disease without having to use plasmapheresis? The advantage of having modern equipment available to easily measure changes in blood hyperviscosity is that it becomes quite easy to evaluate the effectiveness of potential new drug treatments.

**Summary**

- There is significant research evidence that scleroderma is a hyperviscosity syndrome, specifically showing red blood hyperaggregation
- There is research that shows that certain hyperviscosity syndromes can lead to damage to the micro capillaries, leading to some of the typical symptoms that we see with scleroderma
- This suggests that one potential way to control scleroderma progression is to reduce or eliminate the blood hyperviscosity, in lieu of a true “cure” which would stop the disease process before it caused the hyperviscosity to occur in the first place. This is analogous to how anti-retrovirus medications are now used to prevent HIV from developing into AIDS, or how insulin prevents or delays development of diabetes related symptoms.
- The standard method of treating any hyperviscosity syndrome is the use of plasmapheresis. Research done about 20 years ago showed specifically that treating scleroderma patients with a course plasmapheresis significantly reduced blood hyperaggregation for a number of months, resulting in elimination or reduction of some scleroderma specific symptoms, specifically Raynaud’s along with some improvement in skin scores
- The author of this document has been undergoing regular plasmapheresis treatments for more than 19 years to control limited scleroderma. All of the initial symptoms, except for mild Raynaud’s, were eliminated after two years of treatments and I remain in perfect health 22 years after being diagnosed with scleroderma in late 1990. (According to my Internist, in spite of having formally diagnosed limited SD for more than 22 years, I am the healthiest 65 year old patient in his entire practice…) As long as treatments continue, I remain symptom free. If my treatments are stopped or reduced, scleroderma symptoms begin to return within a few months.

**Disclaimer**

The reason for writing this article is to give people in the scleroderma patient community a better understanding of a possible mechanism for how scleroderma
causes the system damage that most of us have experienced or are now beginning to experience. It is not my intent to recommend plasmapheresis as a universal cure-all for scleroderma since it definitely does not, in fact, cure scleroderma at all. There is enough supporting research to advance an understanding of how scleroderma may, in fact, “work” and also why a treatment such as plasmapheresis can in some cases be a method for preventing the progression of the disease and possibly reverse some systemic damage if started earlier enough and continued on a long-term basis.

I would be happy to expand on anything in this post or answer questions directly through email. If you want to reach me, my email address is on my Scleroderma FAQ, located at:

http://www.synnovation.com/sclerodermafaq.html

Ed Harris