Antibiotic Therapy for Systemic Scleroderma

Background

The concept of using antibiotics to treat scleroderma stems from research done initially by Thomas M Brown, MD at the National Institutes of Health, Johns Hopkins and the Rockefeller Institute. Brown used antibiotic therapy to treat a variety of autoimmune diseases based on the theory that arthritic diseases, including scleroderma, are caused by mycoplasma or bacterial infections. Mycoplasmas are essentially bacteria without cell walls and are the smallest complete free-living cellular organisms. Some forms of mycoplasma are known to be the cause of so-called "walking pneumonia." While mycoplasmas are often found in healthy individuals, when someone's immune system is compromised, as can occur with long-standing Lyme disease, for example, mycoplasma and other co-infections are likely to contribute to systemic problems such as autoimmune diseases.

Over the years, Brown and his research partner Harold Clark (as well as other researchers) published a series of case studies that claimed great success in using antibiotics to treat a number of patients with a variety of autoimmune diseases including scleroderma. There are also many anecdotal reports of patients who had not responded to conventional therapy but then had a major improvement in disease symptoms when they switched to antibiotic therapy. The main proponent of the idea that some cases of systemic scleroderma and other autoimmune disorders may be triggered by an infectious process is a group called The Road Back Foundation (see links to their website in the Resources section of this document). Among AP therapy proponents, a frequently cited study is a 2004 study showing that mycoplasma infection induces a scleroderma-like centrosome autoantibody response in mice (Gavanescu, et al. 2004). AP therapy is generally very well tolerated with few side effects. AP therapy advocates often recommend that all patients with connective tissue disorders, including systemic scleroderma, consider this treatment approach initially instead of trying standard, potentially toxic immunosuppressant drug therapies.

On the other side of the controversy, in 2004 a very frequently cited study disputing the efficacy of antibiotic therapy was published with the title "Minocycline is Not Effective in Systemic Sclerosis" (Mayes, et al. 2004). There are a number of serious methodological problems with this study, unfortunately. However, regardless of the validity of the results of this study, since it was an open label study rather than a double-blind placebo-controlled study (the "gold standard" for research studies) any conclusions should be considered preliminary and limited, at best, and do not support the definitive article title indicating that this type of AP therapy is not effective in treating system scleroderma, in the view of this author.

In online discussion forums used by a large number of scleroderma patients, while there are often a few patients who report great success with antibiotic therapy, many other patients who try antibiotic therapy have no changes in symptoms at all, leading many scleroderma researchers and rheumatologists to be very skeptical of this disease model. The traditional view of AP therapy in the medical community is that this is a waste of time and that for a patient with rapidly progressing diffuse scleroderma, for example,

starting the patient on standard therapies that might slow the rate of progression is critical as early in the disease process as possible instead of trying a treatment approach they believe will not be helpful.

Adding to the confusion is the fact that minocycline, often used as the antibiotic of choice when trying antibiotic therapy, is classified by the American College of Rheumatology (and other organizations) as a DMARD (disease-modifying anti-rheumatic drug) and is sometimes used by rheumatologists to help treat autoimmune conditions such as rheumatoid arthritis. However, in standard usage, it is considered as a drug to help control inflammation, not as a drug to potentially treat the underlying cause of an autoimmune disorder.

Analysis and Discussion

The controversy surrounding AP therapy presents a dilemma for many scleroderma patients who read on the Internet that AP therapy may be an effective treatment for systemic scleroderma. However, when they bring this up to their doctors it is dismissed as a fringe treatment idea. On the surface it is hard to reconcile large numbers of case studies and anecdotal reports of substantial reduction of scleroderma symptoms, sometimes including complete remission, with a widely viewed research study (albeit of questionable quality) that shows no difference in skin scores in a group of early diffuse scleroderma patients after a year of treatment with minocycline therapy.

There may actually be a simple way to look at the research data and anecdotal/case study reports that accounts for the widely varying results. This interpretation of the data also suggests specific treatment options and directions for further research that may provide a much clearer understanding of if/when AP therapy should be tried for the treatment of systemic scleroderma.

The general view of the scleroderma research community is that for patients to develop scleroderma, there first must be a genetic predisposition (at this point not yet identified). There also seems to be convincing data to suggest that in some cases of systemic scleroderma, there is a specific triggering event, often years before initial symptoms are visible. For example, a number of studies have found that certain kinds of toxic chemicals, like epoxy resins, solvents, and also silica dust appear to be "trigger events" for a subset of scleroderma patients. While the initial focus of AP therapy proponents was on mycoplasma infections as a potential cause of some cases of autoimmune disorders, in recent years this view has expanded to consider other potential infectious causes in addition to mycoplasma, e.g., H. pylori. In addition, in some patients, a combination of exposure to environmental toxins and infections might be involved in triggering the disease process.

Looking at systemic scleroderma as a family of diseases that require a genetic predisposition but also may have many different potential triggers, some of which may be infectious, the mixed research results make sense. Assuming that only a subset of scleroderma patients have mycoplasma or other infections as their (ongoing) trigger event, then if you try AP therapy on a general population of scleroderma patients, only some of the patients would have any benefit from AP therapy. For example, if the patient's trigger event was exposure to organic solvents, there is no theoretical reason why AP therapy should have ANY effect on their scleroderma symptoms, with the possible exception of the minor anti-inflammatory effects mentioned earlier. This assumption would strongly suggest that any research done on a general group of scleroderma patients might not show significant change in the treatment population as a whole, but an analysis of individual data would show that a subset of the patients

might have significant symptom improvement (patients with infectious triggers) while other patients would show no improvement in symptoms at all (patients with non-infectious triggers).

One interesting but little reported comment from scleroderma patients indicating that AP therapy either put their scleroderma in complete remission or at least substantially improved their symptoms is that their ANA levels often dropped dramatically and in some cases returned to the normal range as their disease went into apparent remission. Normally, in scleroderma the absolute ANA level has almost no correlation with symptom severity, and ANA levels remain relatively stable over time with little variance other than normal lab variance. If an underlying infection is the cause of a patient's scleroderma, and if appropriate AP therapy is able to suppress the underlying infection, then it is theoretically possible that ANA levels could return to normal along with reversal or substantial improvement in symptoms. (It is worth noting here that some organ damage may not be reversible if severe or long-standing even if the underlying disease process is in complete remission.)

Treatment Implications

If the analysis of the research on AP therapy is correct (more on that below), then it makes logical sense for anyone considering antibiotic treatment ideally to begin by being tested for mycoplasma or other potential infections. However, in reality this is difficult to do for a variety of reasons. For example, there are more than 100 recognized species of mycoplasma. Normal lab testing is available for only a small number of these, e.g., M. pneumonia, which is a recognized cause of atypical pneumonia, and M. genitalium, which may be involved in some cases of pelvic inflammatory disease. This suggests that a patient could have a mycoplasma or other infection for which there is no available commercial test that can reliably detect it.

However, there can be a practical benefit of being tested for mycoplasma and other infections, in that detection of such an infection might make insurance coverage of AP treatment more likely. There are a number of labs that do mycoplasma testing, but research data suggests that mycoplasma testing should be done using the Polymerase Chain Reaction (PCR) method, considered the most reliable method of testing. It is worth noting that if patients are considering being tested for mycoplasma or other infections, this testing should be done before starting any treatments using antibiotics since the results will not be accurate once treatments have started. If testing is done and the results are clearly positive, then in addition to being a strong indicator for trying AP therapy, it also provides an objective measure of how effective the treatment is by monitoring the changes to mycoplasma infection levels during the course of treatment.

However, the reality is that patients who decide to try AP therapy often have a difficult time convincing their physicians to try this approach instead of traditional drug treatments. Many rheumatologists don't believe in AP therapy (often based on the single negative research study mentioned above). If the rheumatologist is open to trying AP therapy, it is possible that s/he will not have much experience in understanding optimum AP therapy treatment protocols. The Road Back Foundation (RoadBack.org) has information and support available for physicians. The Road Back Foundation also can assist patients in locating physicians in their area who are experienced in using AP therapy, if their own physicians are not willing to try AP therapy but the patient has made the decision to try this treatment approach.

It is important to note that most anecdotal reporting of successful treatment using AP therapy indicates that it can take six months or more before any improvement is noted, depending on factors such as disease severity, age, duration of disease, and other (non-scleroderma related) medical conditions. This suggests that at least a one-year trial should be considered for AP therapy. This trial period may include trying different antibiotics or combinations of a variety of anti-microbial drugs, since no single antibiotic is effective against all possible infectious organisms. If no improvements are noted by that time, then the likelihood that AP therapy will be effective is significantly reduced.

Also, because of anecdotal reports indicating that ANA levels may drop significantly for patients that report success with AP therapy, it is the suggestion of this author that ANA level be tested (by IFA method only) before starting AP therapy followed by retesting 6 months and one year later, assuming a one-year trial period. Since ANA levels are considered to be stable for scleroderma patients over time, any significant reduction in ANA level during the trial period would be a strong indicator that AP therapy is having a beneficial effect. However, since this potential effect of AP therapy on ANA levels has not been researched, there is no way to know whether a reduction in ANA level is a direct indicator of whether or not AP therapy is having any beneficial effects. Additionally, as was noted earlier in this document, a small percentage of patients with diagnosed scleroderma may have a negative ANA, especially early in the disease, in which case this potential change indicator will not be available.

It is also important to consider that in cases where scleroderma symptoms are progressing rapidly, there is no inherent reason why standard immunosuppressant therapy cannot be combined with AP therapy in order to slow the rate of symptom progression in the short term, while AP therapy might yield more global improvement (in suitable patients) over the long term. A combined approach can make it difficult to sort out which treatment is helping, at least in the short term, but since standard immunosuppressant therapies mostly slow progression of symptoms, if significant improvements are seen in symptoms beyond what would be expected with the standard therapy, it is likely that these improvements resulted from AP therapy.

It is also worth noting that anecdotal reports indicate that patients who achieve significant improvement in scleroderma symptoms, even to the point of complete remission, are not "cured" by AP therapy. This means that patients will likely need to stay on AP therapy indefinitely, probably at a maintenance level, to keep symptoms in remission.

Note for patients and physicians: It is well documented in the literature that some patients who are treated with antibiotic therapy may experience a short-term increase in symptoms during the initial stages of treatment. These symptoms can be mild to severe and are often described as flu-like symptoms, including headaches, joint and muscle pain, sore throat, and chills. This is known as the Jarish-Herxheimer Reaction and is generally considered an immune system reaction to the endotoxins that are released when a large number of disease organisms are suddenly killed off. Originally this reaction was observed in patients treated for syphilis with penicillin. It can also occur when patients are treated with antibiotics for a variety of other diseases caused by bacteria or mycoplasma, including co-infections that frequently occur in Lyme disease

There is some suggestion in the literature that the intensity of the reaction is correlated with the severity of the underlying infection but the research is not clear on this. With patients who have weakened immune systems, they are less likely to show a strong Herxheimer Reaction, for example. The intensity of the reaction may also be related to the level of inflammation the patient is experiencing. Generally the Herxheimer

Reaction occurs within the initial few days of treatment and can last from a few hours to (occasionally) months. Not all patients will experience this reaction and in many cases it will be mild if it does occur. However, since the reaction can be severe enough to cause patients to want to stop AP treatment, patients need to be aware of this potential reaction so they can work with their physicians to support the treatment if a Herxheimer reaction occurs immediately after starting AP therapy.

Research Implications

Given the controversy around AP therapy, additional research is clearly indicated to get a better understanding of the potential role, if any, mycoplasma and other infections play in the development of systemic scleroderma. For example, an initial study could be done to test specifically for signs of mycoplasma infection using PCR in a large pool of scleroderma patients. While this would probably miss some patients who have mycoplasma and other infections that are not being tested for, if a large enough pool of patients with mycoplasma infections can be identified, this would allow for a number of research studies to be done on a subset of scleroderma patients with potential underlying infectious processes as a trigger for their disease.

In addition to looking at common characteristics of such a patient population, it would allow researchers do a double blind AP therapy vs. placebo using a pooled group of mycoplasma positive patients. In addition to obvious objective measures (e.g., modified Rodnan skin score (MRSS) to look at skin changes, PFT scores, etc.), the ANA level should also be tested because of the anecdotal reports suggesting that ANA levels can change significantly or become normal in some patients treated with AP therapy. A study such as this could offer definitive evidence as to the efficacy of AP therapy in scleroderma patients that should theoretically benefit from AP therapy. If the results of this type of study were negative, this would strongly raise questions about whether or not AP therapy is a reasonable treatment option for some scleroderma patients. On the other hand, a strongly positive result would suggest that a focus on developing ways to screen scleroderma patients for possible infectious causes could result in a way to effectively treat this group of scleroderma patients.