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Drug Treatment of Scleroderma

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Contents

Abstract

Scleroderma or systemic sclerosis is a rare condition with many clinical manifestations including Raynaud's phenomenon. As with many other rarely encountered diseases, drug therapy for scleroderma is often empirical with little evidence in the form of randomised controlled trials to aid drug choice.

Raynaud's phenomenon has been recognised for well over 100 years. A considerable number of clinical trials in this area have demonstrated unequivocally the use of nifedipine as a gold standard. Large studies have also demonstrated the efficacy of iloprost. However, this drug is not as yet licensed for scleroderma in the UK or elsewhere. This presents an additional problem as information regarding the use and administration of unlicensed drugs is often sparse and post-marketing surveillance to assess safety is not routinely performed.

When looking at the other distinct conditions encountered by a patient with scleroderma it becomes evident that trials are often retrospective or limited in patient numbers. Studies investigating the use of methotrexate, antithymocyte globulin and cyclophosphamide in patients with scleroderma have been very

small and in some cases not well designed. The major work on penicillamine was a retrospective trial. Again these drugs are not licensed for use in scleroderma.

Drug therapy for pulmonary hypertension secondary to scleroderma closely follows that outlined for primary pulmonary hypertension. In the US there is a patient registry for primary pulmonary hypertension that has enabled well designed, large-scale studies to demonstrate the benefits of epoprostenol in severe primary pulmonary hypertension. Hence, research in this area has progressed considerably over the last decade.

Clearly, a considerable amount of work is being carried out to elucidate new treatment regimens for scleroderma, however, evaluation of these studies is proving to be a difficult process. Designated hospital centres for scleroderma (there are currently 2 in the UK), better markers of disease activity and methods to measure improvement or deterioration in affected organs, should enable research into aetiology, disease progression and treatment to be carried out on a larger scale resulting, hopefully, in more conclusive answers.

The Royal Free Hospital, London, England is a specialist centre for research into and the treatment of scleroderma and related disorders such as Raynaud's phenomenon. There are only approximately 3500 patients in the UK who have scleroderma. The Scleroderma Unit at the Royal Free Hospital looks after over 1200 patients referred from around the UK.

Scleroderma is a multi-system disease with cutaneous, renal, pulmonary, vascular, cardiac and gastrointestinal manifestations. It is a painful and disfiguring condition, which can be associated with an increased mortality. Despite being recognised for over 250 years, knowledge of the pathogenesis is limited and treatment is still directed at symptomatic improvement. Drug therapy of the disease has improved over recent years but as yet there are no drugs that will have a major impact on the progression of severe disease or complications, for example, pulmonary hypertension. This article is a review of the pharmacotherapy for patients with scleroderma. Dosages of many agents used vary from hospital to hospital, and patients tolerate these agents differently requiring individual monitoring and regular assessment. Therefore, specific drug dosages are not included for all agents discussed.

1. Scleroderma

Scleroderma or systemic sclerosis originates from the Greek word meaning 'hard skin'. It is an uncommon disorder with an incidence of approximately 18 per million per year in the UK. Patients have thickened skin on their hands, which may progress to the limbs, face and then the trunk (if the disease is diffuse). This thickening is caused by abnormal collagen deposition in the skin and often results in rigidity with difficulty in moving.

The disease is classed as a clinically heterogeneous connective tissue disorder with Raynaud's phenomenon occurring in more than 90% of patients. The digital arteries and pre-capillary arterioles show marked fibrosis and luminal narrowing. The fibrosis results from excess deposition of collagen produced by fibroblasts. The peripheral vascular disease is associated with platelet activation and abnormal vascular reactivity. However, the situation is often complicated by the fact that Raynaud's phenomenon may be the precursor of systemic illness by more than 20 years. Furthermore, the vasospasm and fibrosis connected with the disease are not confined to the digits but may also involve the heart, gastrointestinal tract, lungs and kidneys.

The immune system is activated in systemic sclerosis with systemic sclerosis-associated antibodies present. These antinuclear antibodies, for example Scleroderma-70 (not seen in all patients), are of particular value in predicting development of interstitial lung disease in the context of scleroderma.[1-3]

1.1 Subsets of Systemic Sclerosis

There are 2 main clinical subsets of systemic sclerosis, classified as limited or diffuse. They are differentiated primarily by the extent of skin involvement.[1]

In limited cutaneous systemic sclerosis, fibrosis is often confined to the face and hands, and most of the disease appears to involve the blood vessels. Patients frequently present with a long history of Raynaud's phenomenon (often of a number of years duration). In addition, there is a significant late incidence of pulmonary hypertension.

Patients with diffuse systemic sclerosis present within 1 year of the onset of Raynaud's phenomenon. Diffuse systemic sclerosis is characterised by excessive fibrosis of the skin, including the trunk area with internal organ and lung involvement. This is the most serious form of the condition. Scleroderma-70 antibodies are present in 70% of patients.[2]

In addition, a pre-scleroderma picture may present as Raynaud's phenomenon with nailfold capillary changes and disease specific antinuclear autoantibodies.[2] Usually patients with pre-scleroderma do not have digital ulcers or pitting scars.

Scleroderma runs a variable course. There have been significant advances in the management of specific organ related complications (see table I), for example, proton pump inhibitors for reflux oesophagitis, broad spectrum antibacterials for small bowel overgrowth and angiotensin converting enzyme (ACE) inhibitors for hypertensive renal crisis. The commonest causes of death in patients with systemic sclerosis are pulmonary hypertension, lung fibrosis and renal disease.[4] Renal complications are now less common because of the use of ACE inhibitors.

The following sections provide an outline of the many conditions encountered and possible treatment strategies.

2. Raynaud's Phenomenon

Raynaud's phenomenon is the blanket term used to describe experiencing cold-related vascular spasm. The disease was first described by Maurice Raynaud in 1862 and occurs in approximately 10% of the population.[5] Raynaud's phenomenon is particularly common in younger women, with over 90% of patients being female and under the age of 25 years.[6]

Raynaud's phenomenon refers to the development of trophic changes as a result of microcirculatory damage and prolonged local ischaemia. Microcirculatory flow may be impeded by activated platelet clumps, rigid red and white cells and damaged endothelium. These damaged vessels release vasoconstricting compounds, which may additionally trigger the clotting cascade and thrombosis. The first symptoms of the disease often present as vasospasm of the digits. However, this vasospasm

Table I. Problems associated with systemic sclerosis and treatment options

Condition	Cause	Potential treatment
Raynaud's phenomenon	Vascular damage	Oral vasodilators
Oesophageal disease	Dysmotility, reflux, spasm	Proton pump inhibitors, cisapride
Mid GI tract disease	Bloating, bacterial overgrowth, diarrhoea	Cisapride, antibacterials
Colorectal/urinary tract disease	Constipation, incontinence	Pelvic floor exercises
Lung disease	Fibrosing alveolitis	Prednisolone, cyclophosphamide
Lung disease and cardiac disease	Pulmonary hypertension	Calcium antagonists, prostacyclin agonists, oral anticoagulants
Cardiac disease	Cardiac failure	ACE inhibitors, digoxin, diuretics
Renal disease	Hypertension	ACE inhibitor
Musculoskeletal	Myositis	Prednisolone, methotrexate, cyclophosphamide, immunoglobulins
Skin disease	Collagen deposition	Emollients, penicillamine

ACE = angiotensin converting enzyme; **GI** = gastrointestinal.

Table II. Drugs to avoid in patients with Raynaud's phenomenon/scleroderma

Peripheral vasoconstrictors
β-Blockers
Ergot alkaloids
Pseudoephedrine
Cytotoxics

may also involve other peripheral areas such as the tip of the nose, tongue and ear lobes.[1,2]

The disease is classically manifested by pallor of the digits followed by cyanosis and rubor. Colour changes of the affected skin can be seen from white to blue to red. The pallor reflects vasospasm, the cyanosis deoxygenation and the rubor, reactive hyperaemia following the return of blood.

2.1 Treatment

In its mildest form, Raynaud's phenomenon might require no treatment at all. Initial management for mild disease focuses mainly on support and advice regarding avoidance of known precipitating factors e.g. vasoconstrictors (see table II), smoking and cold.

In addition, local self help groups can be useful for information and support e.g. the Raynaud's and Scleroderma Society, UK.

Simple vasodilators, e.g. calcium antagonists, may also be of use. Nifedipine has been found to decrease the frequency of vasospasm and severity of attacks in a number of studies.[7] The modified release preparations are preferable as they have a lower incidence of the common adverse effects of headache and flushing. The adverse reactions are due to the central as well as peripheral vasodilatation caused by nifedipine. Capsules are now rarely used and are not recommended because of their rapid effects on systemic blood pressure. Other calcium antagonists such as diltiazem may be of help,[8] whereas verapamil appears to be ineffective.[9]

Nitroglycerin patches may be used in an acute situation at a dose of 0.2 mg/hour (5mg patch) initially increasing to 0.4 mg/hour (10mg patch) if required. The patient should have a patch free period each day to prevent the development of nitrate tolerance.[10]

Levels of serotonin (5-hydroxy-tryptamine; 5-HT) have been shown to be elevated in patients with Raynaud's phenomenon. Theoretically, ketanserin may therefore be of benefit.[11] Ketanserin, an unlicensed drug, is a selective serotonin antagonist with affinity for serotonin receptors on blood vessel walls and platelet membranes. Recently, the Cochrane Collaboration reviewed clinical trials investigating the efficacy of ketanserin and concluded that ketanserin was not significantly different from placebo.[12] In addition, selective serotonin re-uptake inhibitors (SSRIs) and ACE inhibitors may be beneficial (see table III). Angiotensin II receptor antagonists have been trialed in 15 patients and appear to be effective in reducing the vasospastic crises in patients with Raynaud's phenomenon.[13]

Novel treatment schedules include the administration of intravenous prostacyclin analogues, e.g. iloprost and epoprostenol. In some patients, ulceration and gangrene can occur as their disease state progresses and, therefore, intravenous vasodilatation is considered essential.

Studies performed on the orally acting prostacyclin analogues, e.g. cicaprost, proved disappointing. This was possibly due to their low systemic absorption.[14] However, a pilot study with oral limaprost, an alprostadil (prostaglandin E_1) analogue, was more encouraging.[15]

Interestingly some patients have noticed an improvement after changing to a diet supplemented with fish oils and antioxidants. Evening primrose oils and fish oils that can be metabolised to prostaglandin-like compounds should in theory be useful nontoxic agents but convincing evidence of their efficacy is still awaited. Antioxidants, for example ascorbic acid (vitamin C) and tocopherol (vitamin E) may prove useful to decrease free radical-mediated endothelial damage and lipoprotein activation.

3. Gastrointestinal Disease

Gastrointestinal (GI) involvement occurs in the majority patients with systemic sclerosis. Up to 90%

Table III. Possible oral therapy for Raynaud's phenomenon

Drug class	Suggestions
Vasodilators	
Calcium antagonists	Nifedipine SR 20mg bid
	Diltiazem 60mg tid
ACE inhibitors	Enalapril 10mg od
Serotonin antagonists	Ketanserin 40mg od-tid
SSRIs	Fluoxetine 20mg mane
Angiotensin II receptor antagonists	Losartan 25-50mg od
Antioxidants	
Vitamin supplements	Ascorbic acid 1g od
	Tocopherol 400U od
Increasing prostaglandin levels	
Gamolenic acid	Epogam-5 40mg bid

ACE = angiotensin converting enzyme; **bid** = twice daily; **od** = once daily; **SR** = slow release; **SSRI** = selective serotonin re-uptake inhibitor; **tid** = three times daily.

of patients have oesophageal dysmotility. Reflux oesophagitis is common but responds very well to proton pump inhibitors. Prokinetic agents such as cisapride may also be used to increase gastric motility.[16]

4. Pulmonary Disease

4.1 Interstitial Pulmonary Fibrosis

Pulmonary fibrosis, a fibrosis of the alveolar wall, is frequently encountered in patients with systemic sclerosis. Patients with early disease appear to have the greatest likelihood of responding to drug therapy. To date, corticosteroids have been used and it appears that the best results may be observed when they are combined with cyclophosphamide.[17] Recent studies suggest that cyclophosphamide may be effective when given either orally or as intravenous 'pulse' therapy for early alveolitis.[18].

4.2 Pulmonary Hypertension

Pulmonary hypertension is characterised by a progressive elevation of pulmonary artery pressure (>30mm Hg) and vascular resistance, ultimately producing right ventricular failure and death. The incidence of pulmonary hypertension in patients with systemic sclerosis is between 8 and 15% for diffuse and limited disease, respectively.[19] Once pulmonary hypertension is diagnosed, patients have a poor prognosis (if untreated), as pulmonary hypertension is an uncommon disease that is progressive and incurable.

Pulmonary hypertension may be termed primary or 'isolated' in so far as there is involvement of the pulmonary arteries with minimal or no pulmonary interstitial fibrosis. A further distinct form of pulmonary hypertension is secondary to pulmonary interstitial fibrosis. Patients with systemic sclerosis will usually present with secondary pulmonary hypertension. Currently trials have been carried out only in patients with primary pulmonary hypertension. However, this appears to be comparable with secondary pulmonary hypertension seen in patients with systemic sclerosis. Primary pulmonary hypertension is recognised as being associated with a low level of responsiveness to oral vasodilators (approximately 20%)[20] and to progression to right heart failure at a variable and unpredictable rate. The National Institute of Health registry in primary pulmonary hypertension in the US documented a median survival time of 2.8 years after diagnosis.[20]

In the 1980s, interest in the treatment of pulmonary hypertension focused on vasodilator drugs and anticoagulant therapy. In 1992 Rich et al.[19] showed that high doses of calcium antagonists (e.g. nifedipine 60mg 3 times daily) in patients with pulmonary hypertension may improve survival over a 5-year period in those who respond with reductions in pulmonary arterial pressure and pulmonary vascular resistance. However, this view is not universally accepted. Indeed, use of these agents is hampered by frequent worsening of the reflux oesophagitis seen in patients with systemic sclerosis. In addition, the vasodilators appear to be of limited value because their effect on systemic vascular resistance usually equals or exceeds their effect on pulmonary pressure.[19] Anticoagulants can be used to prevent superimposed intravascular thrombosis. At present, high dose continuous prostacyclin analogues are also being investigated

(see section 5). Other possible treatments include ACE inhibitors, which have been found to be effective in decreasing pulmonary vascular resistance,[21] and angiotensin II receptor antagonists, as angiotensin II receptors have recently been found on pulmonary vasculature.[22]

5. Intravenous Vasodilator Therapy

5.1 Epoprostenol (Prostacyclin)

The effects of epoprostenol (prostacyclin) and its chemically stable analogues were first investigated in the treatment of peripheral vascular diseases, for example, Raynaud's disease. Epoprostenol is a potent, short-acting vasodilator and inhibitor of platelet aggregation produced by vascular endothelium. Intravenous vasodilator therapy can prevent or lessen the effects of Raynaud's episodes in patients with systemic sclerosis, increasing blood flow and healing ischaemic digital lesions.[23]

An additional benefit is seen in patients with elevated pulmonary artery pressures.[24] In the US, there is considerable experience using continuous intravenous epoprostenol for pulmonary hypertension with more than 200 patients treated over a 12-year period. Continuous infusions have been associated with a reduction in vascular resistance and increased cardiac output.[25] However, it should be noted that dose requirements increase over time as a result of the development of tolerance by an as yet unknown mechanism. Intermittent intravenous infusions of epoprostenol have been found to increase quality of life and exercise tolerance in patients with severe pulmonary hypertension.[26]

In addition to vasodilatory actions, it appears that abnormalities of increased vascular tone, procoagulability, thrombosis and activation of the immune system might be potentially modulated by epoprostenol therapy.

5.2 Iloprost

Iloprost is a chemically stable synthetic analogue of prostacyclin (a prostacyclin agonist) that decreases pulmonary vascular resistance. It is an unlicensed drug that is available on a named patient basis in the UK for patients with Raynaud's phenomenon and/or systemic sclerosis. Iloprost is longer acting than epoprostenol with vasodilatory properties and platelet inhibitory effects. In addition, it also appears to modulate the immune system by an unknown mechanism.[19,23] A number of double-blind, placebo-controlled studies investigating intravenous infusions of iloprost have shown it to be of benefit in patients with Raynaud's phenomenon and systemic sclerosis.[23] Continuous iloprost infusion may improve exercise tolerance and quality of life in patients with severe pulmonary hypertension associated with systemic sclerosis.[27]

The commonly observed adverse effects encountered when using intravenous vasodilator drugs are headache, nausea, vomiting and diarrhoea. However, a decrease in dose may be implemented if the drug is not tolerated. In addition, premedication with paracetamol (acetaminophen) 1g and metoclopramide 10mg can help to lessen the adverse effects.

Iloprost infusions will almost always be accompanied by a decrease in systemic blood pressure (BP), therefore, it is recommended that BP and pulse should be checked every 20 minutes for the first hour and then hourly for the rest of the infusion.

5.3 Calcitonin Gene Related Peptide

Some patients with Raynaud's phenomenon/systemic sclerosis develop such severe adverse reactions to iloprost they are unable to tolerate the infusions. In these patients calcitonin gene related peptide (CGRP) is being investigated as an alternative.

CGRP is an endogenous peptide and acts as a potent vasodilator. It is abundant in perivascular nerve endings and is thought to be important in controlling blood flow in many organs.[28] CGRP is an unlicensed medication that has only recently been evaluated for use in Raynaud's phenomenon and systemic sclerosis. Indeed in some studies it has been found to be of benefit in these patients.[28-30] A pilot study has shown that CGRP in digital cuta-

neous perivascular nerves is deficient in Raynaud's phenomenon.[29] The exact mode of action of CGRP is unknown. It has been proposed that CGRP may act by increasing cyclic adenosine monophosphate resulting in a decrease in intracellular calcium, smooth muscle relaxation and thus vasodilation.[28] Clearly more work is needed to clarify the exact mechanism.

CGRP is very unstable. It is recommended that the drug should remain out of the freezer for no longer than 72 hours. This narrow temperature window can complicate the administration of a course of treatment.

6. Immunosuppressive Therapy

Because of increasing evidence that immune system abnormalities play a role in the pathogenesis of systemic sclerosis, various forms of immunosuppressive therapy have been investigated. If the diffuse form of the systemic sclerosis is identified early, immunosuppressive agents may prove useful.

6.1 Antithymocyte Globulin

Antithymocyte globulin (ATG) is a polyclonal antibody against human thymocytes and has been used since the 1970s for the treatment of rejection episodes in renal transplant patients. Its use in patients with systemic sclerosis is more controversial. It is thought to produce a temporary suppression of cell-mediated immunity with possible benefit for skin sclerosis, although a high number of adverse reactions to ATG have been noted.

The exact mode of action of ATG in systemic sclerosis is not known. The current view is that activated T cells may contribute to an increase in collagen synthesis by scleroderma fibroblasts. This inappropriate immune response may then lead to vascular lesions characterised by the disease. It has also been demonstrated that T cell infiltrates are present in early scleroderma lesions.[3] A small number of studies have shown ATG to be of benefit in systemic sclerosis.[31] However, Matteson et al.[32] have shown a lack of effect.

When administering ATG, an initial test dose should be given in order to monitor the patient for signs of anaphylaxis (i.e. allergy to rabbit protein). ATG can then be infused on a daily basis. The dose being adjusted according to lymphocyte count, which needs to be monitored daily during treatment. Hydrocortisone and chlorphenamine can be given 1 hour prior to ATG administration to help prevent adverse effects during the infusion. The most common adverse effects being fever, shivering, nausea and malaise. Cytomegalovirus infections have been noted as a result of the prolonged immunosuppressive effect of ATG, which may last for up to 80 days. Daily administration of prednisolone can prevent any associated serum sickness.

6.2 Cyclophosphamide and Methotrexate

Results of studies indicate that cyclophosphamide may decrease the rate of progression of systemic sclerosis and can induce regression of skin and pulmonary organ damage.[33] However, a definitive answer on the efficacy of this drug is still unknown. There is evidence of benefit with the use of cyclophosphamide in combination with corticosteroids in pulmonary fibrosis.[34] A randomised, double-blind trial of methotrexate versus placebo showed an improvement in skin score in patients with systemic sclerosis.[35]

6.3 Cyclosporin

Preliminary data suggests that cyclosporin may be helpful in the treatment of systemic sclerosis.[36] However, the therapeutic potential of cyclosporin is limited by its nephrotoxicity. High doses of the drug have been reported to cause hypertension and renal failure, both of which could be attributable to either the drug or underlying disease.[37]

6.4 Corticosteroids

Long term high dose corticosteroids have a questionable place in the management of systemic sclerosis. They have many potentially toxic adverse effects and are often be implicated in renal

crisis. Therefore, corticosteroid use should be limited to patients with overlapping conditions, for example, myositis.[38]

7. Fibrin Deposition

Fibrotic lesions occur both externally (on the skin) and internally (for example in the lungs) and, in patients with diffuse disease, it may occur very rapidly. Penicillamine affects collagen biosynthesis by interfering with the formation of the stabilising intermolecular cross links and has been used in patients with scleroderma. A retrospective study of 73 patients showed significant improvement in skin sclerosis.[39] Recent evidence would suggest that there is no advantage in using large dosage regimens as the maximum effect may be seen with doses as low as 125mg on alternate days.[40]

8. Future Treatments

The current route of intravenous administration for iloprost limits its usefulness. However, an orally active iloprost formulation has recently become available. Studies are currently being carried out to determine whether oral iloprost has the potential to modify the rate of progression of pulmonary hypertension and to investigate tolerance and safety in patients with systemic sclerosis.

Relaxin is a small, naturally occurring peptide that promotes connective tissue remodelling by inhibiting the production of collagen by fibroblasts and increasing collagen degradation. As one of the key abnormalities encountered in systemic sclerosis is malfunctioning fibroblasts producing excessive collagen, it is hoped that relaxin may be valuable as a potential therapy. Trials using porcine relaxin were performed in the 1950s. More recently, trials with a human recombinant version have been initiated.[41] These studies are small but promising.

Mycophenolate mofetil, a potent reversible selective inhibitor of purine synthesis, inhibits T cell proliferation and antibody production. As there is evidence that T cells play a role in the pathogenesis of systemic sclerosis, mycophenolate mofetil is being investigated for use in early progressive, diffuse, cutaneous scleroderma.

Autologous stem cell transplantation after immune ablation of the host may be a method of modifying the course of the disease in patients with systemic sclerosis. As the risk of developing skin and organ complications is greatest in early disease this time period is the best opportunity for significantly modifying the course of systemic sclerosis before damage to the vital organs has occurred.[42] The critical question is whether the stem cells are already affected by the disease. It might be argued that the genetic susceptibility to developing disease may continue even if the disease is put into remission. However, the genetic component is but one of a number of factors.

9. Conclusion

It is proving extremely difficult to perform randomised, controlled trials in patients with systemic sclerosis as it is a rare, heterogeneous condition with a variable rate of progression. It does appear that the best time for therapeutic intervention is early in the course of the disease. An inherent problem here is that many patients have their disease a number of years before a definitive diagnosis is made.

Although there is no cure for systemic sclerosis, associated complications are definitely treatable. The current aim of treatment being to modify disease progression and improve quality of life. In this respect, drug therapy used to treat the symptoms of systemic sclerosis is improving. As new drugs become available to modify the immune system, in particular the T cells, it will be interesting to see if they are able to make a significant impact on the course of this disease.

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