

Scleroderma

The term scleroderma has been used for both systemic sclerosis, an uncommon multisystem disease characterised by collagen proliferation and fibrosis throughout the body, and for localised fibrotic changes of the skin (morphea) which rarely progresses to involve other organs. In systemic sclerosis, Raynaud's syndrome secondary to vascular involvement usually precedes skin changes; oedema is followed by thickening and tightening of the skin of hands and face, and sometimes limbs and trunk, before progressing to atrophy and contractures. Cutaneous changes may be limited or take a more aggressive diffuse form. Decreased gastrointestinal motility, dysphagia and gastro-oesophageal reflux, arthritis, muscle weakness, and cardiac involvement may occur. Among the most serious potential symptoms, which may result in death, are pulmonary disease and renal failure with malignant hypertension.¹⁻⁷

Many treatments have been tried for localised scleroderma.^{4,5} Symptomatic therapies include emollients and topical and systemic antipruritics. Topical, intralesional, and systemic corticosteroids may be useful, especially in early inflammatory stages. Other treatments include topical and systemic vitamin D analogues, topical tacrolimus, and imiquimod cream. Oral therapies used include ciclosporin, colchicine, hydroxychloroquine, interferon gamma, penicillamine, phenytoin, and methotrexate. Phototherapy with UV light, with or without psoralens, has also been reported to be of benefit.

There is a paucity of adequately controlled studies for systemic scleroderma; no treatment has been clearly shown to affect the progression of the disease, and much management is essentially symptomatic. Immunosuppressants are probably appropriate in the early oedematous stages of diffuse scleroderma.^{1,6,8} Antilymphocyte immunoglobulins have been tried as an induction therapy in early stages of the disease.⁹ Ciclosporin has been found to be beneficial, both for skin and visceral manifestations, but its use has been limited by nephrotoxicity and hypertension.^{1,3,8-10} Tacrolimus has also been tried, though again adverse effects limit its benefit.⁸⁻¹⁰ Mycophenolate mofetil has been tried after antilymphocyte immunoglobulins with reports of significant skin improvement.¹⁰ Cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function, and increase survival, especially in early disease, in a number of studies.⁷ Other novel immunosuppressive strategies include bone marrow ablation followed by peripheral blood stem cell transplantation (see Haematopoietic Stem Cell Transplantation, p.1811),^{1,3,5,8} photopheresis with a psoralen, and the induction of oral tolerance with native bovine type I collagen.⁸ Rituximab is under investigation.¹⁰

Penicillamine has been widely used as an antifibrotic drug, but with variable effects; usual doses proved to be no more effective than lower doses,^{1,8,11} and it is considered by some to be no more effective than placebo.⁵ Interferons alpha and gamma have produced variable results;^{5,8} the latter is under investigation for pulmonary fibrosis.³ Some other drugs have been investigated for their antifibrotic properties, including halofuginone, minocycline and relaxin.^{8,11} There is some evidence that oxidative stress is involved in the pathogenesis of scleroderma, so antioxidants like probucol may also be useful.⁸ Other drugs that have been investigated include potassium aminobenzoate, and thymopentin.

Many patients will require therapy for organ-specific symptoms.

- **Skin flexibility** may be maintained by emollients,¹² and systemic antihistamines can relieve itching, an early feature of diffuse cutaneous scleroderma.⁸ Methotrexate has been used with some benefit.^{1,3,5,7,8,11}
- Most progress has been made in the management of **vascular symptoms**. ACE inhibitors are considered to be the standard treatment for patients with renal ischaemia,^{3,5,6,13} although some 30% of patients will still eventually require renal replacement therapy.⁸ For patients who develop pulmonary arterial hypertension the prostaglandins epoprostenol, iloprost, or treprostinil may be given intravenously,^{1,3,5,6,8} some have also been investigated subcutaneously⁶ or by inhalation.^{3,5,6} Sildenafil or bosentan are also used.^{3,5-7} There is some evidence that epoprostenol and bosentan may be associated with improved survival as well as symptomatic improvement.³ Novel therapies for pulmonary arterial hypertension include ambrisentan⁷ and sitaxentan.^{6,7}

Treatment of Raynaud's syndrome (see under Vasospastic Arterial Disorders, p.1188) unresponsive to nonpharmacological therapy involves the use of calcium-channel blockers such as nifedipine or diltiazem.^{1,3,12} Topical nitrates have been used, and intravenous epoprostenol or iloprost are used in acute attacks.^{1,3,6,8} Oral iloprost has been tried with variable results.⁶ Bosentan can prevent the development of new digital ulcers but may not speed the healing of existing ones.³ Calcitonin gene-related peptide is being investigated as an alternative to iloprost.¹ Because elevated levels of serotonin have been found in patients with Raynaud's phenomenon, SSRIs and ketanserin have been used.¹ Atorvastatin⁶ and sildenafil¹³ have been reported to be helpful. Dietary supplementation with antioxidant vitamins, fish oils, and evening primrose oil has been of anecdotal benefit.^{1,8,14} Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome.^{6,14}

Cardiac involvement may be underdiagnosed;⁸ ACE inhibitors or digoxin may be used.¹

- **Lung fibrosis** is usually treated with cyclophosphamide,^{1,3,5,8,15} with or without a corticosteroid such as prednisolone. There is no evidence for corticosteroids alone in lung scleroderma, and high dose may precipitate scleroderma renal crisis, leading to irreversible renal failure.⁷ As mentioned above, interferon gamma is under investigation.
- In patients with **gastrointestinal disease**, proton pump inhibitors such as omeprazole, sometimes with prokinetic drugs, are extremely effective for oesophageal involvement, and broad spectrum antibacterials are helpful for small bowel bacterial overgrowth.^{1,8}

NSAIDs and corticosteroids must be used with care in scleroderma because of the risk of exacerbating renal and other problems.^{1,8}

1. Leighton C. Drug treatment of scleroderma. *Drugs* 2001; **61**: 419-27.
2. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004; **140**: 37-50.
3. Charles C, et al. Systemic sclerosis: hypothesis-driven treatment strategies. *Lancet* 2006; **367**: 1683-91.
4. Laxer RM, Zulfian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18**: 606-13.
5. Chung L, et al. Systemic and localized scleroderma. *Clin Dermatol* 2006; **24**: 374-92.
6. Kowal-Bielecka O. Targeting vascular disease in systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2006; **6**: 401-7.
7. van Laar JM, et al. Scleroderma lung: pathogenesis, evaluation and current therapy. *Drugs* 2007; **67**: 985-96.
8. Denton CP, Black CM. Scleroderma and related disorders: therapeutic aspects. *Baillieres Best Pract Res Clin Rheumatol* 2000; **14**: 17-35.
9. Morton SJ, Powell RJ. Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma. *Rheumatology (Oxford)* 2000; **39**: 865-9.
10. Lafyatis R. Targeting fibrosis in systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2006; **6**: 395-400.
11. Matucci-Cerinic M, et al. Clinical trials in systemic sclerosis: lessons learned and outcomes. *Arthritis Res Ther* 2007; **9** (suppl 2): S7. Also available at: <http://arthritis-research.com/content/pdf/ar2191.pdf> (accessed 15/04/08)
12. Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004; **18**: 429-62.
13. Moore SC, Hermes DeSantis ER. Treatment of complications associated with systemic sclerosis. *Am J Health-Syst Pharm* 2008; **65**: 315-21.
14. Gaby AR. Natural remedies for scleroderma. *Altern Med Rev* 2006; **11**: 188-95.
15. Tashkin DP, et al. Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354**: 2655-66.

Skin and connective tissue disorders

Immunosuppressants are used in various skin and connective tissue disorders, including Behçet's syndrome (p.1499), eczema (p.1579), pemphigus and pemphigoid (p.1582), polymyositis (p.1510), psoriasis (p.1583), SLE (p.1513), and the various vasculitic syndromes (p.1515). See also Scleroderma, above.

Abetimus Sodium (USAN, #INNM)

Abetimus sódico; Abétimus Sodique; LJP-394; Natrii Abetimusum.

Натрий Абетимус

CAS — 169147-32-4.

ATC — L04AA22.

ATC Vet — QL04AA22.

Profile

Abetimus sodium is an immunomodulator that arrests the production of antibodies to double-stranded DNA. It is under investigation for the treatment of lupus nephritis in patients with SLE.

References

1. Alarcón-Segovia D, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2003; **48**: 442-54.
2. Wallace DJ, Tumlin JA. LJP 394 (abetimus sodium, Riquent) in the management of systemic lupus erythematosus. *Lupus* 2004; **13**: 323-7.
3. Cardiel MH. Abetimus sodium: a new therapy for delaying the time to, and reducing the incidence of, renal flare and/or major systemic lupus erythematosus flares in patients with systemic lupus erythematosus who have a history of renal disease. *Expert Opin Invest Drugs* 2005; **14**: 77-88.
4. Furie R. Abetimus sodium (Riquent) for the prevention of nephritic flares in patients with systemic lupus erythematosus. *Rheum Dis Clin North Am* 2006; **32**: 149-56.
5. Mosca M, et al. LJP-394 (abetimus sodium) in the treatment of systemic lupus erythematosus. *Expert Opin Pharmacother* 2007; **8**: 873-9.

Antilymphocyte Immunoglobulins

Immunoglobulinas antilinfocitarias.

Иммуноглобулины Антилимфоцитарные

ATC — L04AA03 (antilymphocyte immunoglobulin, horse); L04AA04 (antilymphocyte immunoglobulin, rabbit).

ATC Vet — QL04AA03 (antilymphocyte immunoglobulin, horse); QL04AA04 (antithymocyte immunoglobulin, rabbit).

Description. Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes produced by the purification of sera from appropriately immunised animals. The term antilymphocyte immunoglobulin (ALG; lymphocyte immune globulin) implies a product raised against all lymphocyte subsets. The term antithymocyte immunoglobulin (antithymocyte gammaglobulin; antithymocyte globulin; ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). However, in practice the nomenclature does not seem to be used consistently, and both terms tend to be used for antibodies raised against T-cells. Nomenclature normally includes an indication of the animal source of the immunoglobulin e.g. antithymocyte immunoglobulin (horse), or antithymocyte immunoglobulin (rabbit).

In addition to the purified immunoglobulins the native sera (antilymphocyte serum and antithymocyte serum, sometimes referred to as lymphocytic antiserum and thymic antiserum) have also been used as immunosuppressants.

Pharmacopoeias. *Eur.* (see p.vii) includes an anti-T lymphocyte immunoglobulin.

Ph. Eur. 6.2 (Anti-T Lymphocyte Immunoglobulin for Human Use, Animal; Immunoglobulinum Anti-T Lymphocytorum ex Animale ad Usum Humanum). A liquid or freeze-dried preparation containing immunoglobulins, obtained from serum or plasma of animals, mainly rabbits or horses, immunised with human lymphocytic antigens. It has the property of diminishing the number and function of immunocompetent cells, in particular T-lymphocytes. It contains principally immunoglobulin G, and may contain antibodies against other lymphocyte subpopulations and against other cells. It is intended for intravenous administration, after dilution with a suitable diluent where applicable. Protect from light.

Adverse Effects and Precautions

Common adverse reactions to antilymphocyte immunoglobulins include fever, chills, and skin reactions including rash, pruritus, and urticaria, which may be manifestations of hypersensitivity. Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. To minimise fever and chills, the first dose can be infused over at least 6 hours. Dyspnoea, hypotension, chest, back or flank pain may indicate anaphylaxis, which can occur in up to 1% of patients. Fever, pruritus, rashes, myalgia, and arthralgia may represent serum sickness, especially in patients with aplastic anaemia. Use with other immunosuppressants may reduce the incidence or severity of hypersensitivity but increase the risk of acquired systemic infections, such as CMV or herpes simplex. Enhanced immunosuppression may also increase the incidence of post-transplant lymphoproliferative disease or other malignancies.

Leucopenia and thrombocytopenia are also common. Although usually transient, dosage adjustment may be necessary if they become severe or prolonged, and if unremitting, they may warrant stopping therapy. Other adverse effects include dizziness, malaise, headache, abdominal pain, gastrointestinal disturbances, hyper-