INVITED ARTICLE

SYSTEMIC SCLEROSIS

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ABSTRACT

Systemic Sclerosis is a multisystemic disease characterized by sclerosis of the skin and visceral organs, vasculopathy (Raynaud's phenomenon) and autoantibodies. The criteria for the classification of the disease requires either proximal scleroderma (major criteria) or the presence of 2 of the 3 minor features namely sclerodactyly, digital pitting scars and bibasilar pulmonary fibrosis. There are 3 subsets of this condition - diffuse variant, limited variant (CREST syndrome) and Overlap Syndrome (where patients have features of other rheumatic diseases). There are localized forms of scleroderma and pseudoscleroderma states. The presenting features of Systemic Sclerosis are usually Raynaud's, skin changes and arthralgia. Systemic complaints like breathlessness, dyspepsia, etc depending on the organ involved may be present. Management starts with patient education regarding the disease, skin care, exercises and regular medical check-up. There is no miracle cure but much can be done to improve the quality of life of the patient. Nifedepine and other drugs may improve Raynaud's phenomenon. Drugs can be used to treat other complications. Various medication have been tested as disease modifying drugs for scleroderma. These include drugs which inhibit collagen like D-penicillamine, colchicine, and immunosupressive drugs like cyclosporin. Ketotifen, a mast cell stabilizer has been reported to be effective in scleroderma. As it is a relatively safe drug, clinical trials are underway.

Keywords : Systemic Sclerosis, clinical features, treatment

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INTRODUCTION

Systemic sclerosis is, as the name suggests, a condition characterized by sclerosis or thickening. This typically involves the skin (scleroderma) as well as the visceral organs especially the lungs, heart, gastrointestinal tract and kidneys. Two other important features are seen. These are the presence of Raynaud's phenomenon (or vasculopathy) and the presence of autoantibodies.

Scleroderma is the most visible clinical feature but not all patients with thickened skin have systemic sclerosis. The following list of conditions may present with "scleroderma" and we should be aware of them before we make the diagnosis.

1) **Systemic Sclerosis**
   The American College of Rheumatology has suggested a preliminary criteria for classification of Systemic Sclerosis[1]. The presence of the major criteria or the presence of two minor criteria is needed.
   Major criteria - Proximal scleroderma which is thickening of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joint.
   Minor criteria are a) sclerodactyly which is thickened skin involving the fingers only; b) Digital pitting scars; c) Bibasilar pulmonary fibrosis.
   There are three subsets of this condition:
   A) *Diffuse cutaneous sclerosis* - symmetrical widespread thickening of the skin, earlier visceral involvement, presence of tendon friction rub and the autoantibody - antitopisomerase 1.
   B) *Limited disease* - skin changes are limited to the distal extremities and face. There tend to be prominent telangiectasia, calcinosis (CREST syndrome). Visceral involvement tends to be later and the characteristic autoantibody is the anti-centromere antibody.
   C) *Overlap Syndrome* - where patients have clinical features that satisfy the diagnostic criteria of more than one connective tissue disease eg Systemic sclerosis with polymyositis.
2) **Localized scleroderma**
   This is predominantly a skin condition and there are two main types:
   Morphea - plaque like, guttate or generalized
   Linear - includes scleroderma en coup de sabre with or without facial hemiatrophy
3) **Environmental Induced Scleroderma fascitis-related syndrome**
   Vinyl chloride
   Toxic Oil Syndrome - rapeseed adulterated with aniline
   Graft versus host disease
   Cytotoxic drugs - bleomycin
   L-tryptophan in large doses to treat insomnia and anxiety (it is suggested that this is due to contaminant rather than L-tryptohan itself)
   The clues to the diagnosis of these scleroderma-like states are the absence of Raynaud's phenomenon, absence of involvement of the fingers and toes, absence of typical abnormal nailfold pattern and presence of eosinophilia and exteme myalgia[2]. A careful history will often give us the diagnosis.
4) Diseases with skin changes resembling Scleroderma
   Scleredema of Buschke
   Scleromyxedema
   Porphyria cutanea tarda
   Acromegaly
   Amyloidosis
   Phenylketonuria
   Carcinoid syndrome

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CLINICAL FEATURES

Presenting symptoms

The common presenting symptoms are Raynaud's phenomenon, skin changes and arthralgia[3]. The local study based on 19 Scleroderma patients seen in Singapore over an 18-month-period showed that 8 of the patients presented with skin

changes, 6 with joint pains and 2 with Raynaud's phenomenon[4].

Raynaud's phenomenon is extremely common even in a warm country like Singapore. Fourteen of the 19 local patients had Raynaud's. Exposure to the cold (eg in an air conditioned room) or to stress can cause vasospasm. The classical description of fingers turning white, blue and then red may not be seen in all our local patients. The condition can be patchy and mild or very severe leading to digital gangrene. The absence of Raynaud's phenomenon makes one rethink the diagnosis.

Skin Changes are seen in all patients, except in the very rare variant of Scleroderma sine scleroderma where the patient has visceral fibrosis typical of scleroderma but there are no skin changes[5]. It has been reported that the skin fibrosis can follow visceral changes many years later. In the early stages, there is bilateral symmetrical swelling of the skin. Later there is the typical tight hide bound skin. Often in the very late stages, the skin may begin to soften again. The changes in the skin that have been reported in the local series are as follows: proximal scleroderma, sclerodactyly, digital pitting scars, spontaneous ulcerations particularly over the bony prominences, hyperpigmentation, hypopigmentation and telangiectasia. Interestingly, none of the patients in this small group had calcinosis.

Musculoskeletal involvement is a common complaint and the long term problem are the contractures. True synovitis can be seen but is uncommon. Tenosynovitis results in the so called tendon friction rub which is classically seen in the diffuse variant of Systemic Sclerosis. Radiographic changes can be seen. There is soft tissue atrophy, subcutaneous calcinosis and osteolysis with resorption of the terminal phalange and even the radius and ulna.

Muscular involvement is usually wasting and disuse but in those with Overlap Syndrome there is frank inflammatory myositis.

Pulmonary involvement is seen in most of the patients. In the local series, 14 of the 19 patients had evidence of lung involvement. One patient died of respiratory complications. The typical abnormality in Scleroderma is interstitial pulmonary fibrosis. This is easily detected as a diffusion abnormality with pulmonary function testing. Plain CXR may show the bibasilar pulmonary infiltrates. In the late stages the patient will be dysponeic or complain of a dry cough. Pleurisy may be seen and rarely, spontaneous pneumothorax[6]. Pulmonary hypertension is a recognized complication seen particularly in those with the CREST syndrome.

Cardiac involvement is not uncommon and was present in 12 of the 19 local patients. This is typically the patchy fibrosis of the myocardium seen as left or right heart failure which is difficult to treat. The cause is thought to be the small vessel disease, and Raynaud's phenomenon has been demonstrated in the coronary vessels. Right heart failure or Cor Pulmonale, also develops as a result of chronic lung disease.

Gastrointestinal involvement occurs in many patients. Thirteen of the 19 local patients had gastrointestinal involvement. Fibrosis can affect the entire gastrointestinal tract from the esophagus down to the large bowels. Dysphagia is due to reduced peristalsis especially in the lower third of the esophagus. The lower esophageal sphincter pressure is reduced and this leads to reflux and even esophagitis. Decreased motility of the duodenum and less so the stomach, leads to a feeling of epigastric fullness. Small bowel fibrosis result in malabsorption, weight loss and sometimes a clinical picture of the blind loop syndrome. Large bowel involvement can cause pseudointestinal obstruction or just constipation.

Renal involvement has been the dreaded complication which claimed many lives. Six of the 19 local patients had renal involvement and 1 died of acute renal failure. The typical renal crisis is characterized by acute rise in diastolic blood pressure of 110 mm Hg or more, with hypertensive retinopathy of Class III or IV, fits, proteinuria, hematuria, azotemia, microangiopathic hemolytic anemia and hyper-reninemia[7].

Nervous System involvement is uncommon and was not seen in our local series. However, others have reported fits, hemiplegia and cranial nerve palsies due to cerebral infarction. Peripheral neuropathy has been reported and may be due to thickening of the epineurium and perineurium of the spinal roots and the peripheral nerves.

Other organ involvement include Hashimoto's thyroiditis and impotence in the male patients. Sjogren's syndrome (characterized by dryness of the mouth, eyes, vagina) has been seen and there is fibrosis of the salivary glands. Oral cavity involvement is well recognized and is discussed elsewhere.

LABORATORY TEST RESULTS

Most patients with scleroderma have normal blood counts and routine blood tests. The antinuclear antibody test may be present and there are 2 tests which may help to classify scleroderma into the diffuse or the limited variant. The topoisomerase antibody (previously called the Scl 70 antibody) is seen in 33% of those with the diffuse variant. The anti-centromere antibody is seen in 43% of those with the limited variant[8].

All patients should have a full multisystem evaluation to look for visceral involvement.

PATHOGENESIS

The pathogenesis of Systemic Sclerosis is still unknown. There is ongoing research trying to link immunologic, vascular and the fibrotic process in scleroderma. The cells which are the key players are the endothelial cells, fibroblast, T cells, macrophages, platelets and mast cells[9]. Cytokines affect fibroblast proliferation and collagen production and the cytokine shown to increase collagen synthesis is Transforming Growth Factor Beta[10].

MANAGEMENT

There is really NO treatment for Systemic Sclerosis that has been proven effective in well controlled prospective trials. However there is still much that a doctor can do for these patients. Many different drugs have been tried for this condition and these will be discussed. A general guide for the management of these patients is given here.

1) **Establish diagnosis**
   The criteria recommended by the American College of Rheumatology is a useful guide. Consider the differential diagnoses given above.
2) **Multisystem evaluation**
   This is very important as the disease is multisystem. The presence of renal or pulmonary involvement affects the prognosis of the patient adversely. Furthermore, patients with visceral involvement are often treated more aggressively and the problems arising from the organ involvement require treatment too.
3) **Patient education**
   Systemic Sclerosis is a chronic disease and the patient has to understand the disease and participate in his/her health care. He/She must be reassured that though there is no miracle drug, much can be done to help make his/her life more comfortable. He/She has to know simple common sense management of his/her medical problems eg avoidance of cold if he/she has severe Raynaud's and know how to seek help for emergencies. He/She should also learn to live with his/her chronic illness and the occasional periods of depression. A good doctor-patient relationship is important and the same doctor should preferably follow-up the patient.

4) **General Management**

This includes proper care of the dry thick skin, avoidance of harsh soaps, irritating clothes, proper care of skin ulcers. These ulcers are difficult to heal because of the poor circulation. They have to be kept very clean. Clean ulcers may heal faster with special dressings like Hydrocolloid Membrane. Proper physiotherapy, carefully used splints and occupational therapy will help the patient achieve better range of motion and avoid contractures.For the aches and pains, nonsteroidal anti-inflammatory drugs (NSAID's) are very useful. However, care has to be taken in those with renal involvement as NSAID's can cause reversible NSAID nephropathy.

5) **Management of Raynaud's**

For those patients with severe Raynaud's avoidance of cold temperatures is very important. This may mean wearing warm clothes and even gloves at the work places. Sometimes the patient has to transfer to another work place because the temperature is bad for her Raynaud's. In addition, we may have to add drugs if it is problematic. Nifedepine is considered by some to be the gold standard for Raynaud's[11]. However it is not always effective. Other calcium channel blockers like Felodipine and isradipine have been shown to be useful. Topical agents may be tried as sometimes the vasospasm is patchy and if there is systemic side-effects from the calcium blockers eg hypotension and worsening reflux esophagitis due to relaxation of the lower esophageal sphincter pressure. Topical agents reported to be useful are the 1% Glyeryl trinitrate which has been shown to reduce frequency and severity of attacks and reduce ulcer size. Transdermal prostaglandin E2 (PGE2) analogue has also been used successfully. Another oral agent that is useful is Ketanserin[12]. This is a Serotonin S2 receptor antagonist. This has been tested in 222 patients with Raynaud's (79 of whom have Systemic Sclerosis) at 40 mg tds and found to decrease the frequency of attacks. In patients with impending gangrene of the extremities due to severe Raynaud's, i/v pentoxifylline 600mg BD[13] has been shown to be useful. Another intra venous drug found to be of use is Prostaglandin E1. Twelve patients (10 with Scleroderma) showed significant improvement of their Raynaud's and healing of their ulcers[14]. One recent report is very interesting. A lady with Scleroderma suffered an acute myocardial infarct and was given intravenous Recombinant Tissue Plasminogen Activator. Surprisingly her Raynaud's improved, ulcers healed and later even her skin sclerosis got better, suggesting that Tissue plasminogen may have a role in the pathogenesis of Scleroderma[15].

6) **Disease modifying drugs**

Various have been tested in Scleroderma. In general there are two groups - those which inhibit collagen and those which are immunosuppressive.

A) *Drugs which inhibit collagen* are as follows:

N acetyl cysteine has been subjected to a 1-year double blind placebo controlled trial and found to be of no use. POTABA (potassium para aminobenzoate) has anti serotonin and anti fibrosis effect. However, though the early report that 135 cases showed remarkable improvement, it was later found to be of not much use. Colchicine was popular at one time as it depolymerizes fibroblast microtubules and inhibits secretion of collagen and was potentially useful in this fibrotic illness. A report of its use in 19 patients showed that 17 improved and those on a higher dose and with a shorter history of illness did better[16]. However a double blind cross-over study of colchicine 1.2 mg per day for 6 months showed no benefit from the drug. Cyclofenil, a weak estrogen, which decreases the synthesis of proteoglycans and reduces connective tissue synthesis was tested for 6 months. No dramatic improvement was seen but the patients apparently got along better during treatment[17]. D-penicillamine (D-pen) acts to cleave cross linkage of new collagen. A large retrospective study showed that it was indeed useful. They looked at 73 patients who were given D-pen and compared them to 45 patients who were not given the drug. They found that 16% of those given D-pen had new organ involvement while 33% of those not on D-pen had new organ involvement. The 5-year survival was 88% for those on D-pen and 66% for those not on D-pen[18]. Retinoids inhibit normal fibroblast proliferation and reduces procollagen production by normal and scleroderma skin. In one study, 9 of 13 patients who were given isotretinoin 1 mg/kg/day for a period of 6 to 9 months showed improvement in their skin[19]. Recombinant Gamma Interferon down regulates production of procollagen by fibroblast and was tested in 10 patients. They were given 100 µg/day and showed improvement in their skin and musculoskeletal parameter, dysphagia and creatinine clearance[20]. Alpha interferon is a less potent inhibitor of collagen synthesis. Another interesting drug is Ketotifen[21]. This is a mast cell stabilizer and antagonizes mast cells products. The skin of scleroderma patients have been demonstrated to have "phantom mast cells", or actively degranulating mast cells. The tight skin mouse model has been given the drug and improved. There was a report of 2 patients with severe scleroderma who showed dramatic improvement with ketotifen. A prospective controlled study is in progress. The most attractive thing about this drug is its safety profile and easy availability.

B) *Immunosuppressive drugs*

Steroids are useful in the early edematous phase of the disease but do not alter the progress of skin or visceral involvement in the long run. It does improve arthralgia and myositis which are seen in those with overlap syndrome. Azathioprine has been tested on 21 patients and found to be ineffective. Chlorambucil has been subjected to a stringent 3-year double blind controlled study. Unfortunately this drug was also found to be ineffective[22]. Thymopentin is a 5 amino acid sequence that retains the biologic activity of Thymopoietin. Ten patients were enrolled in an open study and 8 showed improvement in Raynaud's and skin thickening[23]. Cyclosporin has been tested in several small studies but the main concern is the possible renal complication. Recently a small study was conducted to test the safety and efficacy of low dose cyclosporin at doses from 1 mg/kg/day to 5 mg/kg/day. Minimal reversible renal toxicity was noted and there was improvement in the skin and musculoskeletal parameters[24]. Methotrexate, a drug increasingly popular in rheumatic therapeutics has been studied. Two open studies have been reported and found promising[25].

C) *Other Therapy*

Other interesting therapeutic modalities include Total Lymphoid Irradiation which was found to be not useful and in fact may worsen the gastrointestinal complications; and Lymphoplasmapheresis which is promising.

7) **Management of Complications**

The management of pulmonary complications begins with prevention. Smoking aggravates the pulmonary fibrosis and the patient must be strongly advised against smoking. D-pen has been shown to improve the diffusion capacity of the lung in scleroderma in a retrospective study[26]. Interestingly POTABA at the dose of 12gm/day for 4.2 years has been reported to reduce the expected decline in the Forced Vital Capacity[27]. The cardiac status may be im-

proved with Nicardipine[28]. Twenty patients were studied and showed improved left ventricular ejection fraction and decreased mean global score. The management of the gastrointestinal complications begin with common sense. Those patients with reflux should be advised against eating a full meal just before bed time and often, elevation of the head of the bed may help relieve symptoms. Histamine 2 blockers and Omeprazole[29] have been found to be useful. In those with blind loop syndrome, cyclical antibiotics have been tried. When all else fail in patients with severe bowel involvement and pseudointestinal obstruction, home central venous hyperalimentation has been used[30]. Renal complications have been treated successfully with Angiotensin Converting Enzyme (ACE) inhibitors. Therapy has improved the survival of patients with renal crisis - 15% 1-year survival if not on an ACE inhibitor and 76% 1-year survival for those given the drug[7]. Not all patients responded, but the improvement in survival is indeed encouraging.

PROGNOSIS

Five-year survival of patients with scleroderma is about 60% (range 34-80%). The 10-year survival is about 47% (range 35 to 74%)[31]. There are factors which may help predict prognosis. The older literature suggests that males, non-white and older patients have poorer outcome. The presence of renal involvement is a bad prognostic feature[32]. Pulmonary and cardiac involvement also adversely affect the outcome. Skin involvement can also be used to predict prognosis. Those patients with diffuse skin involvement have been shown to have a poorer prognosis as compared with those who have limited disease[8]. Recently, it has been shown that it is not just the distribution but also the degree of skin thickening, evaluated as a total skin score, which can predict prognosis. Those with a higher skin score have shorter survival[33].

CONCLUSION

Systemic sclerosis is a difficult condition to manage. Much more basic research is needed to study its pathogenesis and much more clinical research is needed to study drugs shown to be potentially useful for the condition.

References

1. Masi AT, Rodnan GP, Medsger TA et al: Preliminary criteria for the classification Systemic Sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581-90.
2. Jimenez SA : The Eosinophilic-myalgic syndrome and eosinophilic fasciitis. Current Opinions Rheumatol 1990; 2: 960-6
3. Medsger TA : Systemic sclerosis (scleroderma), Eosinophilic Fasciitis and calcinosis. In: Mc Carty DJ.ed. Arthritis and Allied Conditions. 10th Ed. Lea and Febiger, 1985: 994-1036
4. Ng SC, Chew SC : Systemic Sclerosis in Singapore. Abstract presented at the 1st Asian Pacific League Against Rheumatism (APLAR) Seoul Symposium on the Therapy of the Rheumatic Diseases throughout the Asia Pacific Region, Nov 1990
5. Rodnan GP, Fennel RH: Progressive systemic sclerosis sine scleroderma. JAMA 1962; 180: 665-9.
6. Ng SC, Tan WC : Bilateral spontaneous Pneumothorax in Systemic sclerosis - report of 2 cases. J Rheumatol 1990; 17: 689-91
7. Steen VD, Costantino JP, Shapiro AP et al : Outcome of renal crisis in systemic sclerosis : relation to availability of angiotensin converting enzyme inhibitors. Ann Intern Med 1990; 113: 352-7
8. Steen VD, Powell DL, Medsger TA : Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum 1988; 31: 196-203
9. Claman HN : On Scleroderma, mast cells, endothelial cells and fibroblasts. JAMA 1989; 262: 1206-9
10. Gruschwitz M, Muller PU, Sepp N et al : Transcription and expression of transforming growth factor beta in the skin of progressive systemic sclerosis : a mediator of fibrosis? J Invest Dermatol 1990; 94: 197-203
11. Belch JJF : Raynaud's phenomenon. Curr Opinion Rheumatol 1990; 2: 937-41
12. Coffman JD, Clement DL, Creager MA et al : International Study of Ketanserin in Raynaud's Phenomenon. Am J Med 1989; 87: 264-8
13. Goodfield MJD, Rowell NR : Treatment of peripheral gangrene due to systemic sclerosis with intravenous pentoxifylline. Clin Exp Dermatol 1989; 14: 161-2
14. Langevite P, Buskila D, Lee P et al: Treatment of Refractory ischaemic skin ulcers in patients with Raynaud's phenomenon with PGE1 infusion. J Rheumatol 1989; 16: 1433-5
15. Fritzler MJ, Hart DA : Prolonged treatment of Raynaud's phenomenon and scleroderma after recombinant tissue plasminogen activator therapy. Arthritis Rheum 1990; 33: 274-6
16. Alarcon Segovia D, Ramos-Niembro F, De Kasep GI et al: Long term evaluation of colchicine on the treatment of scleroderma. J Rheumatol 1979; 6: 705-12
17. Blom-Bulow B, Oberg K, Wollheim Fa et al : Cyclofenil versus placebo in Progressive Systemic Sclerosis. A 1-year double blind crossover study of 27 patients. Acta Med Scan 1981; 210: 419-28.
18. Steen VD, Medsger TA, Rodnan GP : D-penicillamine therapy in progressive systemic sclerosis (scleroderma), a retrospective analysis. Ann Int Med 1982; 97: 652-9
19. Maurice PDL, Bunker CB, Dowd PM : Isotretinoin in the treatment of systemic sclerosis. Br J Dermatol 1989; 121: 367-74.
20. Kahan A, Amor B, Menkes CJ et al : Recombinant Interferon Gamma in the treatment of systemic sclerosis. Am J Med 1989; 87: 273-7
21. Gruber BL, Kaufman LD : Ketotifen induced remission in progressive early diffuse scleroderma : Evidence for the role of mast cells in disease pathogenesis. Am J Med 1990; 89: 392-5
22. Furst DE, Clements PJ, Hillis S et al : Immunosuppression with chlorambucil versus placebo for scleroderma : results of a 3-year parallel, randomized double blind study. Arthritis Rheum 1989; 32: 584-93
23. Giordano N, Biasi G, Taddeo A et al : An immunomodulatory drug, Thymopentin in the treatment of progressive systemic sclerosis. Clin Rheumatol 1989; 8: 293-4
24. Clements PJ, Paulus HE, Sterz M, Ng SC : A preliminary report on cyclosprin A (CSA) in systemic sclerosis. Arthritis Rheum 1990 (suppl); 33: S66, A147
25. Van der Hoogen F, Rasker J, Van Venrooij W: Treatment of systemic sclerosis with methotrexate : results of a one-year open study. Arthritis Rheum 1990 (suppl); 33: S66, A146
26. Steen VD, Owens GR, Redmond C et al :The effect of D-penicillamine on pulmonary findings in systemic sclerosis. Arthritis Rheum 1985; 28: 882-8
27. Zarafonetis CJD, Dabich L, Devol EB et al : Retrospective studies in scleroderma : pulmonary findings and effect of potassium P-aminobenzoate on vital capacity. Respiration 1989; 56: 22-23
28. Kahan A, Devaux JY, Amor B et al : Pharmacodynamic effect of nicardipine on left ventricular function in systemic sclerosis. J Cardiovasc Pharmacol 1990; 15: 249-53
29. Olive A, Maddison PJ, Davis M : Treatment of esophagitis in scleroderma with Omeprazole. Br J Rheumatol 1989; 28: 553-5
30. Ng SC, Clements PJ, Berquist WE et al : Home Central Venous Hyperalimentation in Fifteen patients with severe Scleroderma Bowel Disease. Arthritis Rheum 1989; 32: 212-6
31. Coppock JS, Bacon PA : Outcome, Assessment and Activity. In: Jayson MIV, Black CM. ed. Systemic Sclerosis : Scleroderma. John Wiley & Sons Ltd Publishers, 1988; 279-88
32. Medsger TA, Masi AT, Rodnan GP et al : Survival with Systemic Sclerosis (scleroderma). A Life-table Analysis of Clinical and Demographics factors in309 patients. Ann Intern Med 1971; 75: 369-76
33. Clements PJ, Lachenbruch PA, Ng SC et al : Skin Score : A semi-quantitative measure of cutaneous involvement that improves prediction of prognosis in Systemic Sclerosis. Arthritis Rheum 1990; 33: 1256-63