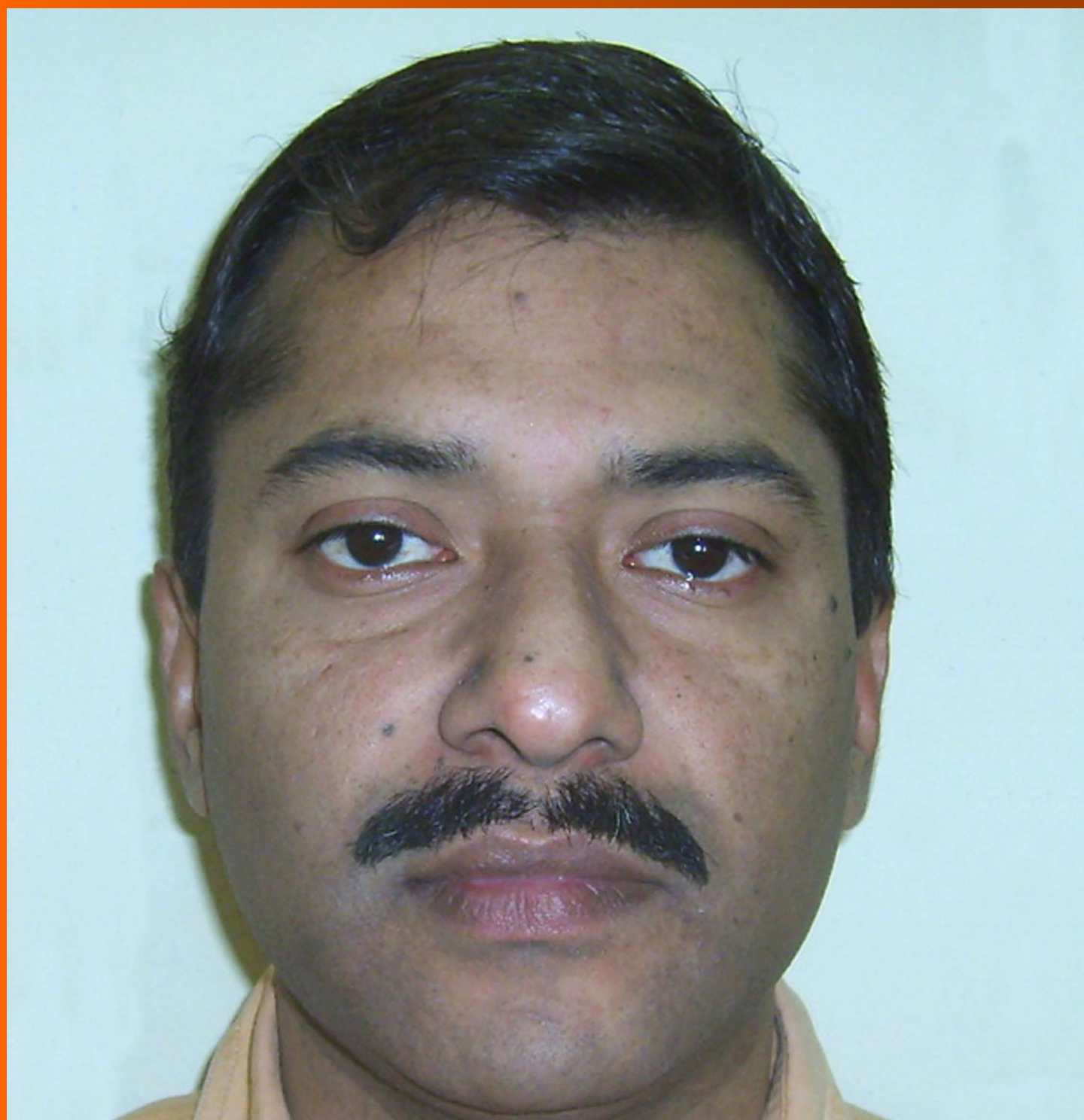


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EDITORIAL

- 127 Epigenetic targets of rheumatoid arthritis
Chabchoub G

REVIEW

- 131 Scleroderma: Not an orphan disease any more
Misra DP, Chowdhury AC, Phatak S, Agarwal V

MINIREVIEWS

- 142 Complementary medicine use in rheumatology: A review
Wong WH, Litwic AE, Dennison EM

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Epigenetic targets of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction. It has a multifactorial aetiology involving both genetic and environmental factors. Epigenetics can be defined as modifications of DNA that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to

histone tails and DNA methylation. Recent evidence has suggested that epigenetic mechanisms may be an important contributor to RA susceptibility. The aim of this editorial is to present evidence for the role of epigenetic mechanisms in the pathogenesis of RA and the potential to therapeutic target. Several studies targeting histone modification and DNA methylation in animal models of inflammatory arthritis will be reviewed and alterations in the epigenetic signature of genes of key RA related pathways such as pro-inflammatory cytokines, proteases and regulators of cellular proliferation.

Key words: Rheumatoid arthritis; Epigenetic; DNA methylation; Histone modification

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Core tip: This paper has highlighted the numerous processes involved in the pathogenesis of rheumatoid arthritis (RA) that are modulated by epigenetic mechanisms. This is important hypotheses to explore a novel therapeutic target in RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction^[1]. A typical feature is the over-production of pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin-1 (IL-1), which lead to up-regulation of other pro-inflammatory molecules and proteases^[2].

RA is a complex disease, and his etiology involves an interaction of both genetic and environmental factors. Genome scans have identified multiple regions

linked to disease^[3-5]. Although interesting associations have been reported^[6,7], only alleles at the HLA-DRB1 locus have consistently demonstrated both linkage and association^[8].

Treatment of RA for most patients involves the administration of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide and sulphasalazine. If DMARDs treatment fails a new drug targets need to be identified to provide therapy for these patients who do not respond to either conventional treatment. Epigenetic mechanisms, which have been implicated in RA, systemic lupus erythematosus and systemic sclerosis^[9,10], offers both new targets for therapy but also may help predict the successful outcome of drug treatments in patients.

EPIGENETICS MECHANISMS

Epigenetics can be defined as modifications of DNA or associated proteins without a change in the DNA sequence itself that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to histone tails and methylation of DNA, which determine the chromatin state and there by access of transcription factors to gene promoter regions. In cells, DNA is packaged by being wound around nucleosome octomers containing two each of histone H2A, H2B, H3 and H4. These histone proteins have N-terminal tails that are susceptible to a number of post-translational alterations including acetylation, methylation, phosphorylation, sumolation, isomerisation of proline and ubiquitination^[11,12].

The most widely studied histone modification is the addition of acetyl groups to the lysine residues of the N-terminal tails of histones H3 and H4. Histone acetyltransferases add the acetyl groups to lysine residues within the histone tails from the donor acetyl coenzyme A. In turn the acetylation can be reversed by histone deacetylases (HDAC).

DNA methylation results from the addition of a methyl group to the 5-carbon position ring of cytosine. The methylation blocks binding of transcription factors and other co-activators to the DNA and recruits transcriptional repressors to the promoter^[13]. Three active DNA methyltransferases (DNMT) have been identified. De novo methylation is performed by DNMT3A and DNMT3B, whereas methylation is maintained following cell division by DNMT1^[14].

EPIGENETIC REGULATION OF IMMUNE CELLS AND PRO-INFLAMMATORY MOLECULES

Both DNA methylation and histone modifications contribute to the expression of a number of T-cell associated cytokines, including interferon gamma (IFN- γ), IL-2 and IL-7R α ^[15-21]. At the IFN- γ promoter differential methylation is seen in naïve, effector and memory T-cells

being highest in naïve cells. There is rapid loss of methylation upon re-stimulation in memory T-cells that is associated with these cells rapid ability to produce IFN- γ in response to reinfection by a virus^[17]. Interestingly, STAT4, which is involved in the stimulation of IFN- γ expression, is also regulated by DNA methylation suggesting that if methylation levels change at both these promoters together there could be a multiplicative effect on the quantity of IFN- γ produced^[18]. Protein kinase C activators and phosphatase inhibitors attenuate DNA methylation levels, possibly by altering the activity of DNMT1, correlating with the induction of IFN- γ providing one possible mechanism for changing methylation levels^[22]. IL-7 is involved in chronic inflammation in RA, not only does it increase osteoclast formation and thereby enhances bone loss but it is also important in maintaining T-cell homeostasis^[23]. Expression of the IL-7 receptor, IL-7R α , on T-cells is regulated by DNA methylation with T-cells showing only low surface IL-7R α having higher methylation at the gene promoter^[21].

TNF is a major player in the pathology of RA confirmed by the efficacy of anti-TNF treatment in many patients. There is increasing evidence that epigenetic mechanisms play a role in regulating TNF expression. Phosphorylation of Serine (S)¹⁰ of histone H3 and demethylation of Lysine (K)⁷ has been observed at the TNF promoter in THP-1 cells, following LPS stimulation^[24]. These changes to the histone code occur in conjunction with loss of heterochromatin binding protein 1 α (HP1 α) from the TNF promoter^[12]. The role of histone acetylation in the regulation of TNF production remains unclear. In animal models of arthritis it appears that HDAC inhibitors attenuate the expression of TNF whereas treatment of monocyte or macrophages with various inhibitors including sodium butyrate, Chlamydocin and HC-toxin generally increased TNF production with sodium butyrate increasing expression levels by 22 fold in THP-1 cells^[24].

Epigenetic regulation has been implicated in the modulation of both IL-1 α and IL-1 β . Methylation of the proximal promoter regulates the expression of IL-1 α and this methylation is responsible for the allele specific expression of this cytokine in CD4⁺ T cells^[25,26]. Histone modifications appear the major epigenetic mechanism regulating IL-1 β . Inhibiting HDAC activity with fibroblasts trichostatin A (TSA) caused an increase in LPS-induced IL-1 β expression in choriodecidual explants^[27]. Interestingly DNA methylation appears to have a role in regulating IL-6 gene expression^[2].

IL-6 is another important pro-inflammatory cytokine involved in the hepatic acute phase of RA and with its role confirmed by the success of the IL-6 receptor antibody, tocilizumab, in reducing disease activity and bone erosions^[2]. Interestingly DNA methylation appears to have a role in regulating IL-6 gene expression. In RA patients reduced DNA methylation at a single CpG site within the promoter (-1099) in comparison to healthy for controls has been identified^[28]. Reduced

methylation at this site was associated with increased IL-6 mRNA production in response to LPS. In addition to the role of epigenetics in regulating expression of pro-inflammatory cytokines, these molecules once produced may also have a role in epigenetic regulation. IL-6 has been shown to modulate the expression and activity of DNMTs leading to increased DNA methylation at the tumour suppressor gene p53 and Foxp3^[29,30]. Methylation induced by IL-6 at the p53 promoter could be playing a role in silencing pro-apoptotic genes in the rheumatoid synovium^[29].

Numerous HDAC inhibitors have been developed mainly to target histone acetylation in RA models. Various studies using topical application of suberoylanilide hydroxamic acid (SAHA), MS-275 and FK228 established their potential to decrease serum IL-6, IL-1 β and TNF levels suggesting an important role for HDAC in regulating production of pro-inflammatory cytokines^[31,32].

EPIGENETIC MECHANISMS AND REGULATION OF THE HOMEOSTASIS IN THE SYNOVIAL JOINT

Increasing evidence suggests that histone tail modifications have an important role in regulating synovial hyperplasia in the RA joint. HDAC inhibitors have been tested in several models of RA in both rats and mice. These studies demonstrated the efficacy of TSA, phenylbutyrate FK228, SAHA and MS275 in ameliorating joint swelling and inflammation associated with inflammatory arthritis^[31-34]. Treatment of RA synovial fibroblasts (RASf) with phenylbutyrate, TSA and FK228 causes histone hyperacetylation at p16^{INK4} and p21^{CIP1} promoters associated with expression of these two proteins which involved in the reduction of RASf numbers^[35]. Interestingly, treatment with TSA and phenyl butyrate established the potential of HDAC inhibitors to reduce paw swelling in an adjuvant arthritis model in rats. It was reported that treatment had to start early for the inhibitors to prevent pannus formation and associated joint damage. In addition, TSA was found to have a greater ability to suppress synovial hyperplasia than phenylbutyrate^[31].

Methylation of DNA may also play a role in regulating cartilage integrity. Demethylation of specific loci within the MMP-3, MMP-9, MMP-13 and ADAMTS-4 promoters is present in cartilage from patients with osteoarthritis compared to controls which, is seen in conjunction with other expression of these enzymes in osteoarthritis cartilage^[36]. Osteogenic protein-1 (OP-1) is a potent anabolic growth factor for articular chondrocytes, an aging-related increase in OP-1 promoter methylation that leads to decreased expression may contribute to cartilage loss seen with aging and in particular with the progression of osteoarthritis in older adults^[37]. In addition, when comparing DNA methylation patterns in chondrocytes and mesenchymal stem cells undergoing

chondrogenesis, loss of methylation at two CpG sites within the promoter of type X collagen is associated with the production of this collagen in the latter cell type^[38]. These findings demonstrate the importance of DNA methylation in regulating the homeostasis cartilage.

CONCLUSION

This editorial has highlighted the numerous processes involved in the pathogenesis of RA that are modulated by epigenetic mechanisms. Key aspects of the production of pro-inflammatory molecules, inappropriate immune cell responses, and abnormalities in the synovium and cartilage degradation have all been shown to be modulated by histone modifications and DNA methylation. However, the complete picture of how epigenetic mechanisms modulate cellular differentiation and response to activation remains unclear. The success of HDAC inhibitors in ameliorating the symptoms of inflammatory arthritis in animal models is an exciting new development for the treatment of RA. Further development in HDAC inhibitors especially as more complete clinical trials, will lead to further knowledge generation on their mechanisms, targets and ability to treat RA.

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Scleroderma: Not an orphan disease any more

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Abstract

Scleroderma (or systemic sclerosis) is a rare disease associated with significant morbidity and mortality. Although previously thought to have a uniformly poor

prognosis, the outlook has changed in recent years. We review recent insights into the pathogenesis, clinical features, assessment and management of scleroderma.

Key words: Pulmonary hypertension; Scleroderma; Interstitial lung disease; Raynauds phenomenon; Fibrosis

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Core tip: Scleroderma is a rare disease associated with significant morbidity and mortality. Better understanding regarding its pathogenesis has led to exploration of various newer therapeutic targets. Anti B cell therapy, endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors and autologous stem cell transplant holds promise in the management of systemic sclerosis. PDE-5 inhibitors in particular have potential to be disease modifying agents as they not only improve Raynaud's phenomenon, but also heal digital ulcers, improve pulmonary hypertension and in addition by virtue of antifibrotic properties may have beneficial effect on skin and lung fibrosis.

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INTRODUCTION

Scleroderma, also known as systemic sclerosis (SSc), is a disease characterized by fibrosis in skin and internal organs, most notably lungs, gastrointestinal tract (GIT), heart, kidneys and muscles. Until a couple of decades back, this rare disorder was associated with a poor clinical outcome, with mortality of up to 70% at 3 years, mostly from respiratory or renal involvement. Advances in understanding of pathogenesis, evolving criteria for early diagnosis and newer therapeutic modalities

provide a new ray of hope in this disease. Herein, we have reviewed recent advances in this field.

PATHOLOGY AND PATHOGENESIS

Scleroderma is characterized by excessive collagen deposition in skin, lungs, esophagus, intestines, heart (muscle and conduction system) and in and around small blood vessels (obliterative intimal proliferation and fibrosis with bland vasculopathy)^[1]. Biopsies of skin show atrophy of the epidermis with increased collagen deposition in the epidermis and dermis. Affected dermal capillaries show obliterative intimal proliferation and fibrosis with bland vasculopathy. Biopsies from lungs of affected individuals show increased alveolar septal thickening with infiltrates of lymphocytes, eosinophils, macrophages and mast cells in the interstitium^[1].

Two factors work in tandem - an inflammatory component with activation of innate and adaptive immunity and autoantibody production, with an additional component of endothelial dysfunction. The inciting event in pathogenesis is not known^[2]. A genetic component is considered likely in view of increased risk of developing SSc (13-19 fold) in siblings and first degree relatives of individuals with SSc. However, lack of significant concordance in monozygotic twins suggests that environmental influences play a significant role in predisposing to SSc^[2]. Candidate gene studies identified polymorphisms involved in T cell signaling (STAT4, TNFSF4, TBX21, NLRP1) and B cell signaling (FAM167A-BLK, BANK and IRAK1) as risk factors for SSc^[2]. Genome wide association studies (GWAS) further confirmed associations with HLA DPB1, DPB2, IRF5 and STAT4, whilst identifying newer genes (CD247 - a co-receptor in B cell signaling; PRORS1C1 - previously identified in psoriasis GWAS studies; rhoB)^[2]. Immunochip studies further implicated genes involved in DNA degradation (DNASE1L3), RNA degradation (TREX-DDX6) and autophagy (ATG5)^[2]. In view of the significant environmental influence on SSc susceptibility, epigenetic modification is proposed to play a major role in SSc pathogenesis^[2]. Global DNA hypomethylation in T lymphocytes and fibroblasts and increased FOXP3 methylation have been shown in SSc^[2]. Decreased histone3 lysine 27 methylation has been demonstrated^[2]. Use of histone deacetylase inhibitor trichostatin resulted in decreased fibrosis in fibroblast cultures by decreasing COL1A1 synthesis, restoring expression of negative regulator of fibrosis FLI1 and inhibiting TGF- β signaling through blockade of Smad3 and 4^[2]. Recently, downregulation of miRNA 30b has been demonstrated in sera of patients with SSc, inversely correlating with skin scores measured using the modified Rodnan skin score (mRSS), possibly acting *via* modulation of PDGF receptor β ^[2]. Increased miRNA 21 (with consequent upregulation of fibrosis related genes COL1A1, COL1A2 and FN1) and decreased antifibrotic miRNAs (miR29a, miR 150, miR 196a, let7a) have been found in patients with SSc^[3-8]. The circulating

profile of free microRNAs in sera of patients with SSc has been found to differ from the sera derived from both healthy controls as well as patients with systemic lupus erythematosus^[9]. Gene profiling in skin biopsies from patients with scleroderma confirmed increased expression of genes in the TGF- β and Wnt pathways, as well those involved in extracellular matrix synthesis and CCN family of proteins (encoding connective tissue growth factor - CTGF). These were expressed to a lesser extent in fibroblasts derived from these skin biopsy specimens, suggesting involvement of other cell types as well^[10]. Hyaluronan levels have been found to be elevated in sera of patients with SSc compared with healthy controls, and these correlated with levels of anti-topoisomerase-I antibodies. This may possibly be of relevance considering that hyaluron acts a ligand for TLR 2 and TLR 4, thereby driving Type I interferon production and autoantibody production in scleroderma^[11].

Environmental factors like exposure to organic solvents, silica, rapeseed oil and l-tryptophan have been implicated in causing skin thickening akin to scleroderma^[1]. Drugs such as bleomycin and pentazocine also cause a similar phenotype. Gadolinium administration in patients with renal dysfunction causes the rare complication of nephrogenic fibrosing sclerosis. Role of viruses (cytomegalovirus, parvovirus B19) has also been postulated^[1].

The inciting event in pathogenesis is endothelial injury, mediated by as yet poorly-characterized environmental influences. This leads on to a leaky endothelium with fluid extravasation (corresponding to the edematous phase of early scleroderma)^[1]. Anti-endothelial cell antibodies have been identified in almost 50% patients with scleroderma, and may drive the endothelial injury. Enhanced release of vasoconstrictors like endothelin 1 and impaired release of prostacyclins causes the endothelial dysfunction, resulting in an exaggerated vasospastic response to cold manifesting as Raynaud's phenomenon (RP)^[12]. There occurs apoptosis of endothelial cells and pericytes, with increased expression of integrins. Chemokines like CCL2 attract inflammatory cells (innate cells like macrophages, secreting type I interferons, and adaptive immune cells - T and B lymphocytes). Nucleic acid from damaged cells is taken up by macrophages and other antigen presenting cells, and presented to T cells by means of B cells, causing their activation to a Th2 phenotype (secreting interleukin-4, -5, -13) and Th17 cells^[1,12]. Simultaneously, B cells also differentiate to form plasma cells, and further form autoantibodies. Autoantibodies to centromeric proteins (specifically centromeric protein B - CENB), topoisomerase I and RNA polymerase III are identified in almost two-thirds of patients with SSc, and are mutually exclusive^[1]. The reparative process induced by this tissue damage is dysregulated, and involves excessive fibroblast activation. These fibroblasts may be derived from endothelial or epithelial cells (epithelial or endothelial to mesenchymal transformation), resident tissue fibroblasts or circulating pericytes. Th2 cytokines

Table 1 American College of Rheumatology 1980 criteria for systemic sclerosis

Major criterion	Minor criterion
Scleroderma like skin change proximal to MCP or MTP joints	Sclerodactyly Digital pitting scars of fingertips or loss of distal finger pad Bibasilar Pulmonary fibrosis

(IL-4, IL-13), chemokines like CCL2, excessive platelet derived growth factor (PDGF) receptor, stimulating agonist antibodies to PDGF receptor, increased thrombin, endothelin 1 and TGF- β levels in the milieu ultimately lead to increased signaling *via* the TGF- β receptor^[1,12]. Oxidative stress resulting from release of reactive oxygen species further drives augmented profibrotic signaling *via* Ras and ERK1/2, *via* a self-reinforcing loop. These culminate in increased collagen and alpha-smooth muscle actin (α -SMA) synthesis as well as production of connective tissue growth factor (CTGF) and surface receptors for PDGF and TGF- β ^[1,12]. Hypoxia resulting from vasculopathy drives excessive production of angiogenic factors (PDGF, CTGF, VEGF) and the resulting neoangiogenesis is disordered^[1,12].

Animal models of SSc help further our understanding of these pathogenic processes *in vitro*^[13]. The four key components of SSc pathology are vasculopathy, fibrosis, inflammation and autoimmunity, and these are captured in different animal models. Induced models involve immunization of mice with bleomycin and topoisomerase I (lack vasculopathy), angiotensin II (lack autoimmunity), collagen V and models of graft-vs-host disease involving immunization of RAG knockout mice with splenocytes from B10.D2 mice (encompass all features of SSc)^[13]. Spontaneous models include the Tsk 1 mice (spontaneous mutation in fibrillin 1) and Tsk 2 mice (which have all the features except vasculopathy), constitutively active TGF- β receptor I and II (all features except autoimmunity) and UCD 200/206 model in chicken (encompassing all features of human scleroderma)^[13].

CLASSIFICATION CRITERIA

In 1980, the American College of Rheumatology (ACR) had proposed the preliminary classification criterion for diagnosis of SSc (Table 1)^[14].

Either 1 major or 2 or more of the minor criterion had to be fulfilled for a patient to be classified as SSc. This criterion had 98% specificity but it lacks sensitivity as it was developed using patients who had long standing SSc. Later on with the advent of nailfold capillaroscopy and scleroderma specific antibodies it was found that this criterion is unable to detect a subset of patients with early disease and those who lacks skin changes. In 1988, LeRoy *et al*^[15] proposed new criteria that included clinical features, autoantibodies, and capillaroscopy results, highlighting the differences

between the 2 main SSc subsets. In 2001 revision of the classification criteria was proposed by LeRoy and Medsger^[16] for the early diagnosis of SSc using nailfold capillary pattern and SSc-related autoantibodies. However neither the 1980 ACR criterion nor the LeRoy criterion was sensitive enough to diagnose very early/early phase of SSc. Internal organ involvement may be present from the earliest stages of SSc even before skin involvement- this necessitates that the diagnosis of SSc be made in the very early or at least early phase so that therapeutic options may be considered early^[17,18]. In 2008-2009 experts from 85 EUSTAR (EULAR Scleroderma Trial And Research) centers participated in a Delphi exercise to develop criterion for the Very Early Diagnosis Of Systemic Sclerosis (VEDOSS)^[19]. Three domains containing seven items were identified as follows: skin domain (puffy fingers/puffy swollen digits turning into sclerodactyly); vascular domain (RP, abnormal capillaroscopy with scleroderma pattern) and laboratory domain (antinuclear, anticentromere, and antitopoisomerase-I antibodies). In 2013 following consideration of the definition of early SSc, the ACR and European League Against Rheumatism (EULAR) jointly proposed a new criteria for the diagnosis of SSc (Table 2)^[20].

The criterion was tested in a validation cohort -sensitivity and specificity were 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ACR classification criteria. The 2013 ACR criterion was tested in another cohort of 724 patients by the Canadian Scleroderma Research Group (CSRG) -sensitivity was consistent in subgroups of patients with lcSSc (98.8% vs 85.6%), anti-centromere antibodies (98.9% vs 79.8%), disease duration \leq 3 years (98.7% vs 84.7%) or no skin involvement proximal to the metacarpophalangeal joints (97% vs 60%)^[21]. The recent ACR classification criteria enable earlier diagnosis of patients, when the disease course may be potentially more amenable to modification with therapy.

AUTOANTIBODIES

Anti-Topoisomerase I /Scl-70 antibody (ATA), anti-centromere antibody (ACA) and anti-RNA polymerase III (anti-RNAP III) are the three major autoantibodies in SSc, mutually exclusive and present in about 70% patients with SSc. Each of these are associated with distinct clinical phenotype^[22]. ATA are associated with diffuse cutaneous involvement (although 30% patients can have limited cutaneous disease) and increased risk of interstitial lung disease (ILD) and mortality^[22]. Anti-RNAP III antibodies are also associated with diffuse skin involvement and higher risk of scleroderma renal crisis (SRC), but lesser risk of ILD^[22]. ACA are associated with limited skin involvement, oesophageal dysmotility, calcinosis and pulmonary hypertension^[22]. The presence of ACA in a patient with primary Raynaud's predicts future development of limited cutaneous SSc (LCSSc). Lesser prevalent antibodies include antibodies to Th/To

Table 2 American College of Rheumatology/European League Against Rheumatism criteria for diagnosis of systemic sclerosis (2013) (Reproduced with permission)

Item	Sub-item(s)	Weight/score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy Fingers	2
	Sclerodactyly of the fingers (distal to the 4 metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nail fold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon		3
SSc-related autoantibodies [anticentromere, anti-topoisomerase I (anti-Scl-70), anti-RNA polymerase III] (maximum score is 3)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

(limited skin involvement with severe ILD, SRC and poorer survival), anti-fibrillar antibodies (severe Raynaud's and pulmonary hypertension) and anti-U11/U12 RNP antibodies (severe ILD)^[22].

CLINICAL FEATURES

Skin tightening in SSc characteristically is proximal to the metacarpophalangeal or metatarsophalangeal joints. Rarely, SSc can occur without skin tightening (only having Raynaud's, digital ulcers, ILD or gastrointestinal manifestations in conjunction with autoantibodies), when it is called as SSc sine scleroderma^[23]. When it is limited to areas distal to the elbow, knees or only involves the face and neck, the disease is characterized as limited cutaneous systemic sclerosis (lcSSc). More distal involvement of the extremities or skin tightening over the chest and trunk is defined as diffuse cutaneous systemic sclerosis (dcSSc). It is important to know these subsets due to characteristic differences in presentation and prognosis, as subsequently discussed^[24]. Skin tightening is quantified clinically using the mRSS, wherein 17 areas are assessed (bilateral arms, forearms, hands, fingers, thighs, legs and feet; face, chest and abdomen anteriorly) and graded between 0 to 3 (0 if skin is normal and 3 if there is hide-bound skin)^[24]. A greater mRSS portends a worse prognosis^[25]. Skin tightening tends to resolve with time, and patients with advanced disease may have atrophic skin with lack of subcutaneous fat. Hence patients with dcSSc, when seen late at a time when most of the skin tightening has resolved, may be mistakenly classified as lcSSc^[24].

The most characteristic feature of SSc is RP, which is defined as an exaggerated vasospastic response of the extremities to cold exposure^[26]. It typically involves the fingers and toes, which during a classical attack of Raynaud's progress through phases of pallor, cyanosis and reactive erythema (triphasic or complete Raynaud's). More commonly, the patient describes any two of these

three color changes (incomplete Raynaud's)^[26]. RP is a major cause of morbidity in patients with SSc. Raynaud's can be primary, usually affecting young females, with negative autoantibodies and younger age of onset, or secondary, when it occurs in conjunction with connective tissue diseases like scleroderma or mixed connective tissue diseases^[26]. Secondary Raynaud's is usually associated with antinuclear antibody positivity, nailfold capillary changes of dilated capillary loops (in the early phase) and capillary dropouts (in the later stages) and is often severe enough to cause digital ulcerations, digital pulp loss, resorption of distal portion of phalanges and digital gangrene. It is a manifestation of endothelial dysfunction in SSc^[26]. Patients with lcSSc usually have onset of RP a few years prior to onset of skin tightening, whereas those with dcSSc have onset either concurrent with or just preceding skin tightening^[26]. Abnormal angiogenesis is clinically manifest as telangiectasias in the skin, and stomach (gastric antral vascular ectasias or watermelon stomach); can result in severe upper gastrointestinal bleeding^[1].

The most common cause of morbidity and long term mortality in SSc is pulmonary involvement. Usually, this is in the form of pulmonary fibrosis, in a non-specific interstitial pneumonia pattern, affecting up to two-thirds of patients with dcSSc and a third of lcSSc patients^[12]. Clinically, patients present with insidious onset of exertional dyspnea, fatigue and dry cough. A good screening test is reduction in forced vital capacity (FVC) below 70%, which further mandates a high resolution computerized tomogram (HRCT) of the thorax to document the extent of pulmonary involvement. Early changes include ground-glass appearance of the lung fields, followed progressively by fibrosis, traction bronchiectasis and honeycombing^[27-30]. Pulmonary hypertension (PH) can result consequent to hypoxia resulting from ILD or it can occur *de novo*, more commonly in long-standing lcSSc (up to a fourth of patients at 10 years)^[27-30]. Recently emerging

biomarkers of ILD include lysyl oxidase, tenascin-C, thrombospondin 5, CXCL-5 in serum, and CXCL2, CXCL4, S100A8/9 in bronchoalveolar lavage. Positivity for ATA or anti-Th/To antibodies has been linked to development of ILD in SSc^[27-30].

As described above, pulmonary hypertension can occur *de novo* (usually in lcSSc) or consequent to ILD. Pulmonary function testing may show a disproportionate reduction in TLCO (diffusion capacity for carbon monoxide) compared to FVC, and a ratio of percentage predicted FVC to percentage predicted TLCO of greater than 1.6 has been proposed as a screening tool for further evaluation regarding PH^[31]. Transthoracic Doppler echocardiography shows elevated right sided pressures, with a right ventricular systolic pressure (RVSP) of greater than 40 mmHg proposed to diagnose pulmonary hypertension^[31]. Notably, resting pressures may be normal and right sided pressures may only be elevated during exercise, when the patient becomes short of breath. An elevation of RVSP should be confirmed with a right heart catheterization to document pulmonary arterial pressures, as well as to assess responsiveness of right sided pressures to calcium channel blockers^[31]. Apart from PH, SSc can affect the heart due to fibrosis involving the conduction system (manifesting as conduction blocks, paroxysmal atrial tachycardia or rarely ventricular arrhythmias), myocardium (diastolic dysfunction, myocarditis) or pericardium^[31]. Usually pericardial effusions are mild; moderate to severe symptomatic effusions portend a grave prognosis with increased mortality at 1 year. Cardiac involvement accounts for a third of deaths associated with SSc^[31].

SSc involves much of the gastrointestinal system from the mouth to the anal canal. Luminal effects of the disease process are usually more common and symptomatic than effects on the hepatobiliary system and pancreas. The gastrointestinal manifestations add considerably to disease related morbidity^[32]. About half the patients affected are symptomatic, while a vast majority has asymptomatic disease^[32].

The clinical features and principles of management revolve upon the pathogenesis and site of disease. Like the skin, the GI tract also faces dysfunction of the small blood vessels producing ischemia and fibroblast proliferation producing collagen deposition. However, as a general rule throughout the lumen, smooth muscle dysfunction is the mechanism more relevant to production of symptoms^[32]. Smooth muscle pathology in SSc goes through "stages": An early stage of neural dysfunction which produces smooth muscle "paresis" and dysmotility. The reason of the neural dysfunction is under debate but has been postulated to be an autoimmune process^[33]. In this stage, the smooth muscle itself is not weak and therefore may be amenable to prokinetic medications. The later stage constitutes one of smooth muscle atrophy, which does not respond much to drugs. The absorptive surface - the villi- are usually unaffected^[33].

Involvement of the esophagus is usually the most clinically evident GI manifestation. The lower esophagus is more affected than the upper^[34]. Symptoms of acid reflux are common when the lower esophageal sphincter is incompetent as a result of smooth muscle dysfunction. On the other hand, dysphagia may be seen in patients with diffuse esophageal spasm. In a patient with prominent regurgitation, disappearance of heartburn and a new onset dysphagia may herald a stricture forming in the area chronically exposed to acid^[34]. Lower esophageal manometry is a sensitive investigation and has a role in diagnostic dilemmas^[34]. Management involves Proton pump inhibitors in reflux disease; calcium channel blockers are best avoided. Strictures are usually amenable to endoscopic dilatation. An unusual manifestation in the esophagus is "esophageal Raynaud's" which refers to cold- induced vessel vasospasm producing pain^[34].

Gastric involvement is rarely symptomatic. Patients may have ectasia of the vessels (GAVE) which can cause blood loss and anemia. The patient may present with functional worsening of respiratory status. Small intestinal disease is mainly because of abnormal electrical activity in the smooth muscles. Patients present with abdominal pain which occurs due to stasis and intestinal dilatation due to ineffective peristalsis^[35]. A smaller number of patients present with symptoms suggestive of malabsorption- steatorrhea, diarrhea and weight loss. This is seen mainly in patients with bacterial overgrowth in dilated segments, possibly due to bacterial interference in micelle formation^[36]. While radiography with luminal contrast demonstrates dilated intestinal loops, a positive glucose H₂ breath test in a patient with chronic diarrhea suffices to make a diagnosis of SIBO^[37]. Treatment entails rotational antibiotics- commonly used regimens include trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin-clavulanate. Liver disease is relatively rare and represents an overlap phenomenon; usually with primary biliary cirrhosis. However, the prognosis is better than PBC and rarely progresses to end-stage liver disease^[38]. Often, simple modes of treatment provide considerable symptomatic relief such as facial exercise in tight mouth and dietary modifications in amount and timings of meals^[38].

Renal involvement is life threatening in SSc, and goes by the eponym of SRC. Typically, SRC occurs on a background of diffuse cutaneous disease^[39,40]. Presence of antibodies to RNA Polymerase III or treatment with steroids (greater than 15 mg prednisolone equivalent daily) increases the risk of developing SRC. The pathogenesis involves endothelial injury in the renal microvasculature, resulting in platelet aggregation and thrombotic microangiopathy with concomitant obliterative vasculopathy^[39,40]. Reduction in renal blood flow causes hyperreninemic hyperaldosteronism, resulting in hypertension, creatinine elevation and acute kidney injury. A rise of blood pressure greater than 20% above the baseline should ring the warning bells in patients with SSc, although in up to 20%, SRC can be

normotensive^[39,40]. Urinalysis shows proteinuria with or without hematuria and casts. Peripheral smear shows thrombocytopenia with fragmented red cells resulting from microangiopathy. A few decades back, SRC was associated with a mortality of greater than 80% at 1 year and a high proportion of dialysis dependence^[39,40]. The advent of angiotensin converting enzyme (ACE) inhibitors has revolutionized the therapy of SRC, with greater than 80% survival at 3 years. ACE inhibitors should be started immediately when SRC is suspected, and supportive care provided with maintenance of electrolyte balance and renal replacement therapy if needed^[39,40]. An initial rise in serum creatinine may occur on starting ACE inhibitors in such patients; however this should not dissuade further use of the se agents and they should rather be continued with caution. Often, patients with SRC appropriately treated with ACE inhibitors regain baseline renal function by 6 to 18 mo^[39,40]. In addition to SRC, patients with SSc who develop renal impairment may do so due to glomerulonephritis resulting from overlap with lupus, or pauci-immune glomerulonephritis resulting from overlap with ANCA vasculitis. The clinician needs to have a high index of suspicion to diagnose appropriately such overlap. Such scenarios should be suspected in the presence of active urinary sediments with serologic evidence of lupus or ANCA-associated vasculitis and require a renal biopsy for diagnosis^[39,40]. They should be treated with immunosuppression as in the context of lupus or vasculitis^[39,40].

Musculoskeletal involvement may be in the form of tendon friction rubs, which are usually felt in the long flexor and extensor tendons around the wrist or anterior compartment tendons of the leg^[12]. They portend a grave prognosis with increased risk of subsequent SRC. Patients can have a symmetric inflammatory polyarthrititis of upper and lower limbs affecting small and large joints, treated in the same way as inflammatory arthritis in the context of rheumatic diseases. There can be myositis, either clinically evident as neck, trunk and proximal weakness, or subclinical with only muscle enzyme (creatinine phosphokinase, lactate dehydrogenase, aspartate aminotransferase or alanine aminotransferase) elevation and electromyographic/biopsy evidence of inflammatory myositis^[12]. Such patients with polymyositis-scleroderma overlap usually have antibodies to PM-Scl, and an overall better prognosis. Long standing SSc can result in muscle and joint contractures which are a major cause of morbidity^[12].

A proportion of patients with SSc may not have skin tightening (systemic sclerosis sine scleroderma). Such patients tend to be male and have less severe digital ulcers and telangiectasias^[23]. Almost 80% have oesophageal dysmotility and more than half of these patients have evidence of interstitial lung disease^[23].

OUTCOME MEASURES

Health related quality of life in patients with SSc can

be assessed using the SF-36 questionnaire and Health assessment questionnaire-disability index^[41]. A modified version of the HAQ has been devised for patients with SSc (Scleroderma HAQ - SHAQ) and includes visual analog scales (VAS) for 5 domains - general health, Raynaud's, digital ulcers, dyspnea and gastrointestinal manifestations. These are rated on a scale of 0-15 and normalized to the nearest whole number between 0 and 3 to facilitate inclusion in the HAQ^[41]. Other tools used are the Patient Reported Outcome Measures Information System and United Kingdom functional scale^[41].

Measures of hand involvement include finger-to-distal palmar crease distance, an easily measurable index reflecting severity of impairment of hand function. Quantitative scales like Cochin Hand Mobility Scale and Hand Mobility in Scleroderma Scale are generally used in the setting of clinical trials^[42,43]. Oral involvement in the setting of SSc (limited mouth opening, dryness resulting from sicca syndrome) can be quantified using the Mouth Handicap in SSc scale^[44]. Pulmonary hypertension is quantified by right heart catheterization to measure pulmonary arterial pressures or measuring RVSP on transthoracic Doppler echocardiogram. Functional limitation due to the same can be assessed using the 6-min walk test and Borg dyspnea scale. Interstitial lung disease is measured using extent of involvement on HRCT thorax, VAS for dyspnea (as a component of SHAQ) and Mahler transitional dyspnea index. Severity of gastrointestinal involvement can be measured in day-to-day clinical practice using the VAS for gastrointestinal involvement as a component of the SHAQ, and in a clinical trial setting using the detailed questionnaire devised by the University College of Los Angeles (UCLA SCTC GIT 2.0). RP is measured by documenting frequency and severity of Raynaud's attacks, documenting new-onset digital ulcers, VAS for Raynaud's on the SHAQ and the Raynaud's Condition Score (RCS)^[41].

MANAGEMENT

The management of SSc shall be considered under the various subheadings regarding management of Raynaud's, ILD, PH, skin fibrosis and gastrointestinal involvement.

RP AND DIGITAL ULCERS

RP and digital ulcers are the most dramatic features of SSc, and often the most distressing. They account for significant morbidity in these patients. Hence management of RP in SSc is an area of active research. Dihydropyridine calcium channel blocker nifedipine (10-20 mg three times a day) has been proven efficacious in management of RP in a meta-analysis^[45]. Angiotensin receptor blockade with losartan (50 mg/d) has also been proven in RCTs to be comparable to nifedipine for this indication^[46]. Intravenous iloprost (0.5-3 ng/kg per minute continuous infusion for 3-5 d,

repeated at intervals of 6-8 wk) has shown efficacy in improving RP as well as preventing new digital ulcers in randomized trials^[47], however its use is limited by need for hospitalization, cost and availability. Oral dual endothelin receptor blockade with Bosentan (62.5-125 mg twice daily) has failed to improve RP but has shown efficacy in preventing onset of digital ulcers. However, it delayed the healing of existing digital ulcers^[48].

Our group has done pioneering work in studying the role of phosphodiesterase-5 (PDE-5) inhibition in RP associated with SSc^[49]. PDE-5 is a molecule involved in degradation of cyclic GMP (c-GMP), and its inhibition results in vasodilation due to persistence of action of c-GMP on the smooth muscle of the vasculature^[49]. We studied the role of oral tadalafil at a dose of 20 mg alternate day in refractory RP due to SSc, as add-on to prior therapy with nifedipine or losartan, in a cross-over randomized controlled trial design, and demonstrated efficacy in reduction of frequency and severity of Raynaud's attacks and improvement of RCS^[49]. Surprisingly, pre-existing digital ulcers healed quickly and it prevented development of new digital ulcers^[49]. A meta-analysis of PDE-5 inhibition for secondary Raynaud's (which included data from two trials done at our centre) concluded significant benefit in decreasing frequency and severity of Raynaud's attacks as well as improvement in RCS^[50]. These findings have reflected a change in clinical practice regarding the management of SSc-related RP, with the recent guidelines from the Scleroderma Clinical Trials Consortium (SCTC) and CSRG recommending PDE-5 inhibition as a second line therapy for this indication failing initial therapy with calcium channel blockade^[51]. In our experience, use of PDE-5 inhibitors has significantly reduced morbidity due to RP and digital ulcers in our patients with SSc, especially during the winter months.

INTERSTITIAL LUNG DISEASE

SSc-associated ILD is a major cause of morbidity and mortality. Randomized trial evidence on this field is sparse. Two landmark trials published in 2006 explored the role of cyclophosphamide in SSc-ILD. The Scleroderma Lung Study compared oral cyclophosphamide (at a dose up to 2 mg/kg) for 1 year vs placebo in patients with SSc-ILD with FVC less than 70% and HRCT evidence of fibrosis^[52]. There was a small (2.5%) improvement in FVC on oral cyclophosphamide compared with a worsening on placebo therapy. In the subset with dcSSc, improvement in skin thickening was also demonstrated. Both groups did not differ significantly with respect to adverse events^[52]. This effect was maintained until 18 mo and was lost by 24 mo in the absence of further immunosuppression, suggesting need for maintenance immunosuppression therapy^[53]. Another study compared the role of intravenous cyclophosphamide at monthly doses of 600 mg/m² for 6 mo with oral prednisolone (20 mg alternate day) followed by azathioprine with placebo in SSc-ILD. Although the

findings did not reach statistical significance, there was a definite improvement of FVC by 4% in the group receiving intravenous cyclophosphamide^[54]. A comparison of oral cyclophosphamide vs mycophenolate mofetil in SSc-ILD is currently under study (Scleroderma Lung Study II - clinicaltrials.gov identifier NCT00883129). A recent publication from the EUSTAR group demonstrated potential benefit of rituximab in preventing progression of lung fibrosis in SSc based on retrospective data^[55].

PDE-5 inhibition, in addition to vasodilation, has also shown a role in improving endothelial cell dysfunction and favorably affecting vascular remodeling in animal models of pulmonary hypertension. Also effects in decreasing activation of TGF- β activation and ameliorating fibrosis in bleomycin-induced pulmonary fibrosis have been reported^[56,57]. This led us to hypothesize whether PDE-5 inhibition can be a therapeutic modality in SSc-ILD. A recently-concluded double-blind, randomized placebo controlled trial of tadalafil 20 mg every alternate day vs placebo in SSc-ILD conducted at our centre showed significant improvement in patient-reported breathing scale, and a trend towards improvement in pulmonary function, breathing VAS and physician-assessed breathing scale (Abstract number 1679, ACR Annual Conference 2014)^[58]. These promising results suggest potential use of PDE-5 inhibition in SSc-ILD.

Pulmonary hypertension

Since most patients with SSc-related PH have poor response to calcium channel blockers during right heart catheterization, the same are not recommended for PH in SSc^[59]. Endothelin-1 is a key molecule identified in the pathogenesis of vasculopathy in SSc^[12]. Randomized controlled trials support use of non-selective endothelin receptor antagonist bosentan (at doses varying from 62.5 to 250 mg twice a day)^[60,61] and the selective endothelin receptor A antagonist sitaxentan (at doses from 50 to 300 mg once a day)^[60,62,63] in patients in SSc-associated PH. Newer oral endothelin dual receptor antagonist (macitentan) at doses of 3 or 10 mg od was found effective in connective-tissue disease-related pulmonary hypertension^[64]. PDE-5 inhibitors have been widely used in treatment of PH. Shorter acting PDE-5 inhibitor sildenafil (at doses of 20, 40 or 80 mg thrice daily or 50 mg twice or thrice daily) has been proven efficacious in treatment of PH in the setting of SSc^[65,66]. The disadvantage of short half life and hence frequent administration of sildenafil is overcome by using tadalafil (t_{1/2} 17.5 h) at a dose of 40 mg daily, which has shown efficacy in SSc-related PH^[67]. In patients with NYHA Class *de novo* dyspnea (breathlessness at rest), intravenous epoprostenol therapy has been demonstrated to cause significant symptom relief. However its use is limited by need for continuous intravenous administration and rebound worsening on sudden withdrawal of therapy^[68].

Skin fibrosis

Unfortunately, medical therapy for skin fibrosis has not

been effective. Studies on skin tightening in response to therapy have to be interpreted with caution due to the fact that skin tightening spontaneously resolves in a majority of patients with time. Studies on use of methotrexate have provided conflicting data^[69,70]. However the EULAR recommendations mention methotrexate as a possible option for skin involvement in SSc^[71]. Although cyclophosphamide, azathioprine, mycophenolate mofetil and cyclosporine have been reported to benefit skin tightening in SSc, isolated skin involvement is seldom an indication for their clinical use^[71]. Recent studies have proposed a role for B-cell depletion therapy for reduction of skin involvement in SSc, however results from anecdotal reports and small case series has been conflicting^[72].

Gastrointestinal involvement

Dryness of mouth is managed using sugar-free chewing gums, advise regarding oral hygiene, frequent brushing of teeth (including after meals), taking frequent sips of water and use of parasympathomimetics like pilocarpine and cevimeline. Patients with restricted mouth opening are advised to take small frequent, semisolid, energy-rich meals^[32]. Esophageal dysmotility is managed in addition by use of proton pump inhibitors to reduce acid secretion in the stomach and prokinetic agents like metoclopramide, domperidone and itopride. Intestinal small bowel overgrowth is managed by use of rotational courses of antibiotics like quinolones^[32].

Recent studies have shown a beneficial role of hematopoietic stem cell transplant in early severe SSc compared to placebo. The recent Autologous Stem Cell Transplantation International Scleroderma trial^[73] showed that although autologous hematopoietic stem cell transplant was associated with greater mortality at 1 year, longer term follow up at 5.8 years showed a survival benefit compared to intravenous cyclophosphamide. The trial investigators recommended use of less intense conditioning regimens in future studies to attempt reduction of the early mortality.

Despite advances in understanding of pathogenesis and early diagnosis and interventions, outcomes have not changed overall in SSc in the last 40 years, with a still unacceptably high standardized mortality rate of 3.5^[74]. Cardiac and pulmonary diseases remain major causes of death^[74].

CONCLUSION

With active research ongoing with respect to pathogenesis and newer emerging therapeutic modalities, scleroderma is no more an orphan disease. PDE-5 inhibitors and endothelin receptor antagonists are emerging as drugs with substantial benefit in management of SSc. The day does not seem far when there will be an efficacious disease-modifying agent for SSc.

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Complementary medicine use in rheumatology: A review

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Abstract

Complementary and alternative medicine (CAM) use is increasing worldwide; specifically it appears that these

treatment modalities are popular among rheumatology patients. The most commonly reported CAM therapies are herbal medicines, homeopathy, chiropractic, acupuncture and reflexology. Despite high reported rates of CAM use, the number of patients disclosing use to their rheumatologists remains low. This review highlights rates of current CAM use in rheumatology in studies performed worldwide, and discusses potential reasons for nondisclosure of CAM use to clinicians.

Key words: Complementary medicine; Alternative medicine; Rheumatology; Arthritis; Acupuncture

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Core tip: Complementary and alternative medicine is widely used among rheumatology patients, who often do not inform their consultants that they are using such therapies. This may reflect a fear that clinicians may not approve, or a lack of awareness that the information may be helpful in their management. Increased awareness of the issue, and better education of clinicians and patients is beneficial.

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COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine (CAM) was defined by Ernst *et al*^[1] as "diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frame works of medicine" Although the terms "com-

Table 1 Usage of complementary and alternative medicine in European Countries^[17]

Treatment	Prevalence of reported use across Europe (%)
Herbal medicine	5.9-48.3
Homeopathy	2-27
Chiropractic	0.4-28.8
Acupuncture	0.44-23
Reflexology	0.4-21

plementary and alternative" are often used together, their meanings differ; according to the United States National Centre for Complementary and Alternative Medicine (NCCAM), "complementary" refers to using non-mainstream treatment alongside conventional medicine, to better cope with a health condition, whereas "alternative" means using non-mainstream treatment in place of conventional medicine to treat a health condition^[2]. A "complementary therapy" may provide a patient with an experience that is pleasant in itself, and improves the patient's ability to cope with a chronic health condition; as the term implies, these therapies are designed to be used alongside conventional therapy. By contrast, an "alternative" therapy is designed to be used in place of conventional treatment. Few studies have examined the mechanism of action of these treatments, although some researchers have postulated an effect on immune function, and invocation of the placebo effect. Many therapies discussed here can be used in either way; homeopathy, acupuncture, chiropractic and osteopathy have been used within either a "complementary" or "alternative" framework.

CAM is often classified into 3 groups: (1) professionally organised alternative therapies such as acupuncture, chiropractic, herbal medicine, homeopathy and osteopathy; (2) complementary therapies, such as aromatherapy, massage, yoga, meditation, hypnotherapy, Alexander technique, shiatsu, reflexology and counselling stress therapy; and (3) alternative disciplines, for example, traditional Chinese medicine, traditional Indian medicine (Ayurveda), anthroposophical medicine, naturopathy as well as crystal therapy, dowsing, iridology and kinesiology^[3].

Documentation of CAM use in rheumatology is important because of potential adverse consequences in some groups of rheumatology patients. For example, spinal manipulation applied by chiropractor therapists among rheumatoid arthritis (RA) patients with atlanto-axial instability may result in neurological complications^[4]. In addition, herbal medications used in CAM may interact with prescribed rheumatology medications^[5].

ROLE OF CAM IN RHEUMATOLOGY

There is some evidence to suggest efficacy of CAM in rheumatic conditions such as osteoarthritis (OA), RA and other types of arthritis^[6-11]. In a recent systematic review

that assessed the efficacy of CAM in the management of OA, capsaicin gel and S-adenosyl methionine were shown to be effective in improving pain in this group of patients^[7]. Another study suggested that acupuncture and massage therapy were effective in reduction of OA related pain^[6]. Finally, in other work administration of rosehip (herbal medicine) was associated with reductions in OA pain compared to placebo^[8]. Macfarlane *et al*^[9] recently undertook a study aimed to evaluate the evidence supporting or refuting CAM use in the treatment of RA and reported that borage seed oil and thunder god vine reduced symptoms in RA. Practising Iyengar yoga was shown by another group to have a beneficial effect on symptoms of RA^[10]. Acupuncture has been demonstrated to be efficacious in crystal arthritis^[11]. However, other studies have suggested that the evidence supporting the effectiveness of CAM in RA and OA is more doubtful^[12]. Hence the literature around the efficacy of CAM in rheumatology is hotly contested, and studies that consider CAM use are often advertised widely and hence more readily available to patients. The efficacy of CAM in rheumatology is not the focus of this review, which aims rather to highlight the widespread use of these therapies in rheumatology patients.

PREVALENCE AND PATTERNS OF CAM USE IN RHEUMATOLOGY

The prevalence of CAM use in the general population is high according to studies worldwide^[13-15]. The prevalence of CAM use is reported to be the lowest in England when compared to other European countries, United States, Australia and Japan^[16]. The top 5 most commonly reported CAM therapies in the European Union are: herbal medicines, homeopathy, chiropractic, acupuncture and reflexology (Table 1)^[17].

Specifically, CAM usage is popular in rheumatology^[18]. Several studies have suggested a high prevalence of CAM use in North America and Australia in rheumatology patients^[19-22]. The highest prevalence of CAM therapy use in rheumatology patients (94%) was reported in a study by Kronenfeld *et al*^[19]. The 3 most popular modalities reported in this study were topical treatments, dietary modification and supplementary vitamins. In another survey of 232 rheumatology patients in the United States, two thirds had used CAM^[20]. Chiropractic therapy was found to be the most popular and most helpful treatment modality. Patients who had OA were more likely to use CAM regularly. In another OA cohort of patients who were followed for 1 year, 44% of patients remained non-users throughout, whereas 12% started CAM, 22% maintained, and 22% stopped use of CAM^[21]. Equal numbers of patients started and stopped using electric stimulators and visiting chiropractors during the study period. Although patients most frequently started herbal remedies, dietary supplements and special diets, a similar number discontinued these therapies, suggesting that use of

Table 2 Reasons for not disclosing usage of complementary and alternative medicine to rheumatologists

Physician did not ask
Patient thought it unnecessary to talk about it
Patient feared negative response from physician
Patient had used CAM before seeing physician
Patient forgot to discuss

CAM: Complementary and alternative medicine.

CAM is often transitory. Another study of RA patients found that nutritional supplements and touch therapies (massage, acupuncture and acupressure) were the most widely used in this patient disease group, with mind body techniques more prevalent among younger patients^[22]. CAM modalities were found to be used in conjunction with mainstream conventional treatments in early as well as later stages of the disease. CAM usage is also popular among Canadian rheumatology patients; in a study of 235 rheumatology patients, 60% of them had ever used CAM remedies and 79% of these patients had used CAM remedies in the previous 12 mo. The study also found that 47% of these patients had tried at least one CAM before their first rheumatology consultation. Results from a nationwide survey in Canada demonstrated that 22% adults with arthritis over 20 years of age had used CAM^[23]. In this group chiropractic services were used most commonly (59.5%) followed by massage (48.5%), acupuncture (25%) and homeopathy (21%).

CAM is also used widely by rheumatology patients in the Middle East. Patients attending rheumatology clinics in Israel tended to use CAM more often compared to patients seen in primary care, internal medicine and other specialties^[24]; this study indicated that in Israel, CAM was used more frequently by patients with fibromyalgia (58%), in contrast to studies from other countries, where the most common rheumatological diagnoses associated with CAM use were RA and OA^[25-28]. In work from Eastern Europe, a study from Turkey reported that 76% ($n = 250$) patients with any form of arthritis used at least one CAM^[25]. Most of them used thermal therapy, similar to a comparable study from the United States^[29].

Finally, CAM use is also common in Australasia; in one Australian study 82% of RA patients, used more than one CAM after diagnosis and more than half of respondents were current users^[30]. The report suggested the most common CAMs used in Australia were dietary manipulation and use of copper bracelets. In contrast, studies in Asian countries suggest other therapies are commonly used. For example in India, Ayurveda and massage therapy were used most commonly (around 80%) in one survey^[28]. This may be because the Government of India strongly supports alternative therapies such as Ayurveda, Homeopathy, Siddha and Unani medicine and CAM practices and modern (allopathic) medicine in India run in parallel^[31]. Similar

observations have been made in Korea, where traditional oriental medical treatment is performed by certified Korea medical doctors and there is a wide acceptance of acupuncture as a basic treatment^[32]. By contrast, Japan has a lower prevalence of CAM use (approximately 35%). In Japan, dietary supplements, particularly ginger extracts were the most popular type of CAM^[33].

USERS OF CAM, PATIENTS' REASONS AND OBJECTIVES FOR USING CAM

There is a documented variation in the use of CAM among different socio-demographic groups. Women are more likely to use CAM than men^[21,23,24,27,29]. There are also differences according to age: middle aged people are most likely to use complementary therapies, while the youngest and oldest age groups are less likely to have done so^[23,25,27,29,34]. Ethnic background appears relevant in CAM usage among adults with arthritis; Caucasian individuals are more likely to use CAM than Blacks, Asians and Hispanics^[21,34,35]. In recent studies, the use of CAM was explored according to three socio-economic indicators. Researchers reported that the use of CAM increases significantly with income, and higher education in most western countries^[23,24,34]. This may be because medical insurance does not cover CAM, and hence low-income population groups may not be able to afford it^[24].

The aims of trying CAM in rheumatology patients is most commonly reported to be to reduce and control pain and stiffness^[20,27,36]. Similarly a wide range of reasons have been suggested for discontinuation of CAM therapy, with the lack of effectiveness and high cost of therapy being most common^[21]. A common source of information about CAM is by "word of mouth", *e.g.*, previous experiences from families, relatives, neighbours and friends^[24,25,27].

DISCLOSURE OF CAM USE TO RHEUMATOLOGISTS

The reported rate of patients disclosing CAM use to rheumatologists ranges from 28% to over 70%^[20,28,32,36-40]. Women are more likely to talk about CAM therapy than men^[37,38]. In one study, rheumatology patients diagnosed with fibromyalgia were more likely to discuss use of CAM with their physician^[20]. When asked directly, many patients suggest that they would welcome and greater involvement of their clinician in providing details of alternative practitioners when requested^[39].

REASONS FOR NOT DISCLOSING USAGE OF CAM TO RHEUMATOLOGISTS

There are various reasons documented for patients not disclosing their CAM use to clinicians (Table 2). Some patients are concerned about a possible negative

response from rheumatologists. This includes the fear that rheumatologists would not continue to provide health care to them or that the rheumatologist would disapprove of them using CAM. Patients may also want to avoid any conflict or embarrassment during their consultation, and may feel that non-disclosure would ensure this^[39,40]. Most rheumatologists do not ask specifically about CAM usage and this may give an impression that the disclosure of the use of CAM is not important in their health care treatment^[20,40]. Sleath *et al.*^[38] suggested that rheumatology patients were more likely to disclose CAM if the rheumatologists involved them in the decision-making process about their treatment and treatment goals.

ATTITUDES OF RHEUMATOLOGISTS TOWARDS CAM

A recent study suggested that physicians in the United Kingdom have a positive attitude towards some CAM modalities^[41]. Among a background prevalence of use of CAM ranging from 12.1% to 32%, 39% to 46% of physicians recommended using CAM.

Similarly, a national survey of rheumatologist in the United States showed that more than half of the respondents considered some CAM therapies to be beneficial and were at least moderately likely to recommend them to the patients^[42]. Female rheumatologists were significantly more likely than men to perceive common CAM therapies as beneficial. Rheumatologists born outside the United States had more favourable attitudes towards CAM overall. Out of 345 rheumatologists, 65% were "very" or "somewhat likely" to recommend body work, followed closely by meditation (64%). Only 10% of them would consider recommending an energy medicine modality, such as Reiki. This could reflect limited availability and experience of this therapy. Massage had the highest perceived benefits, followed by meditation. Acupuncture and spinal manipulation was thought to be either "very" or "moderately" beneficial, whilst 60% of the rheumatologists had indicated that glucosamine and/or chondroitin was not very or at all beneficial.

Another study looked at the referral patterns for 22 CAM therapies^[43]. It showed that half of physicians had referred patients for 8 of the therapies (*i.e.*, acupuncture, behavioural medicine, biofeedback, counselling/psychotherapy, dietary prescriptions, electromagnetic applications such as transcutaneous and percutaneous electrical nerve stimulation, exercise and massage). Counselling/psychotherapy and exercise headed the list of modalities which had been used by more than half of the rheumatologists. However other modalities including meditation, prayer and spiritual direction non-chiropractic, hypnotherapy, herbal medicine, music therapy, magnets, energetic healing and homeopathy were never used by 75% of physicians.

These findings were subsequently supported by a systematic review, which concluded that rheumatologists

in North America showed moderate acceptance towards some types of CAM, particularly body work and meditation practices^[44]. An overwhelming majority of them had recommended these therapies in the past and were willing to continue this practice. That review also indicated that energy medicine had the lowest perceived benefit and received least recommendations and referrals from rheumatologists. A large proportion of rheumatologists had reported no or minor clinical use of CAM therapies such as prayer, spiritual direction and herbal medicine. They believed that the efficacy of these modalities is poor and potentially even harmful.

CONCLUSION

CAM usage is substantially increasing worldwide. Despite high rates of use of CAM therapies the number of patients disclosing it to their rheumatologists is low. There is a need to promote disclosure, particularly with respect to over the counter preparations that may interact with physician prescribed medication.

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