

Management of mixed connective tissue disease

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Mixed connective tissue disease (MCTD) is a systemic autoimmune rheumatic disease manifesting as specific clinical features in the presence of antibodies reactive with the extractable nuclear antigen U1-ribonucleoprotein. It has been described across geographic and ethnic groups. The exact prevalence of MCTD is unknown, but it is usually less common than systemic lupus erythematosus, but more common than systemic sclerosis or dermatomyositis in the populations reported. The clinical features most often present in those with MCTD include: arthralgias/arthritis, Raynaud's phenomenon, decreased esophageal motility, decreased pulmonary diffusing capacity, swollen hands and myositis. The therapeutic plan for MCTD needs to be tailored to the specific clinical manifestations present in each patient. Particular attention should be given to early recognition of pulmonary involvement.

Mixed connective tissue disease (MCTD) is a systemic autoimmune rheumatic disease first identified by the combination of specific clinical features and the presence of novel antibodies reactive with an extractable nuclear antigen now known as U1-ribonucleoprotein (RNP) [1]. The clinical features most commonly reported in MCTD include: arthritis/arthralgias, Raynaud's phenomenon, decreased esophageal motility, decreased pulmonary diffusing capacity, swollen hands and myositis.

Several classification criteria schemes have been described for MCTD. Among one of the most widely utilized is that proposed by Alarcon-Segovia [2]. This requires the presence of at least three clinical criteria (one of which must be either synovitis or myositis) and one serologic criteria, specifically, the presence of anti-RNP antibodies. The possible clinical criteria include: swollen hands, synovitis, myositis, Raynaud's phenomenon and sclerodactyly/acrosclerosis.

The exact prevalence of MCTD is unknown, but it has been described across geographic and ethnic groups, and typically is less common than systemic lupus erythematosus (SLE), but more common than scleroderma or dermatomyositis in the population being reported [3]. The female:male ratio appears similar to the approximate 9:1 female:male ratio of SLE. Ratios as high as 16:1 have been reported [4]. There is a clear genetic contribution to disease susceptibility, as MCTD has been linked to HLA-DR4 in studies from several continents [5,6].

Although the original description of MCTD observed a favorable prognosis, there is now the realization that some patients can have organ

involvement patterns that can lead to substantial morbidity and mortality. Pulmonary manifestations, in particular pulmonary hypertension, are the major cause of mortality in MCTD. A 29-year follow-up of MCTD from the University of Missouri, Columbia (MO, USA) cohort found approximately one in five patients had died from pulmonary hypertension or its sequelae [7]. The 15-year survival was estimated at 89.6% in a Hungarian cohort of 179 patients [8]. Of the 12 patients dying during follow-up, five died from pulmonary arterial hypertension (PAH). Distinct from SLE, significant renal disease and neurologic disease are not major manifestations in MCTD, as was originally reported by Sharp *et al.* [1].

Treatment of MCTD

There are no US FDA-sanctioned treatments for MCTD, and there is also a dearth of trial-based evidence for the management of MCTD, so many of the interventions used derive from treatments for the other connective tissue diseases. In general, basic initial management includes interventions such as vasodilators for Raynaud's phenomenon, medication to relieve arthralgias and proton-pump inhibitors for gastroesophageal reflux. However, managing MCTD is a significant challenge to the clinician, with the treatment plan crafted to address the particular clinical features significant in each case.

Arthralgias & inflammatory arthritis

Patients can have arthralgias and/or fatigue secondary to their underlying MCTD – limited time courses of low-dose corticosteroids (prednisolone

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typically at doses no higher than 10 mg/day or equivalent) can often be helpful, particularly for acute exacerbations of these symptoms. Antimalarials, particularly hydroxychloroquine, are the agents most often employed in those with chronic symptoms. Hydroxychloroquine is used in doses similar to those in which it has demonstrated to improve outcomes in SLE, with a maximum dose of 6.5 mg/kg/day [9]. NSAIDs are also useful for control of arthralgias. The lowest effective dose should be used and the patient evaluated for potential gastrointestinal and cardiovascular risk factors.

Inflammatory arthritis is another of the common early manifestations of MCTD. It is usually a nonerosive arthritis with prominent pain and stiffness components [7]. Eventually, a small proportion of patients can develop deformities, which may be fixed or reducible, consistent with a Jacoud's-type arthropathy. Occasionally, an erosive arthritis can develop, which may be similar to that found in rheumatoid arthritis; however, this is uncommon [10].

A substantial number of patients, in some cases more than 50%, test positive for rheumatoid factor, and some may be initially diagnosed as having rheumatoid arthritis (RA) [11]. The proportion of patients with MCTD that have antibodies directed at cyclic citrullinated peptides (anti-CCP antibodies) has not yet been fully elucidated. A Japanese group reported 9% of a group of 86 patients with MCTD testing positive for anti-CCP antibodies [12]. A distinguishing feature is that most patients with MCTD, unlike RA, will have Raynaud's phenomenon [13].

MCTD patients with inflammatory arthritis can benefit from symptom-relieving medications such as NSAIDs. Antimalarials, such as hydroxychloroquine (<6.5 mg/kg/day), can be effective, as they are in SLE. Short courses of low-dose corticosteroids such as prednisolone at 10 mg/day or lower can be very helpful in controlling articular flares. If the patient requires continued corticosteroid therapy or has evidence of deforming or erosive arthritis, methotrexate therapy (oral or subcutaneous) should be considered [14]. As a result of the pulmonary involvement associated with MCTD, one should be diligent in monitoring for methotrexate-related pulmonary injury. Leflunomide has been used with success in RA, but has not been tested in MCTD. Other steroid-sparing agents, such as azathioprine, can be tried, but have not been shown to be superior to methotrexate in the management of inflammatory arthritis. There is

significant experience using azathioprine in MCTD [15] and related diseases such as SLE [16]. Clinical trials have demonstrated efficacy for preventing disease progression for some aspects of SLE [16].

TNF blockade has been utilized with great clinical efficacy in RA, psoriatic arthritis and ankylosing spondylitis, but not in SLE, where antinuclear antibody induction and rare cases of drug-induced lupus have been reported [17]. Use of this therapy resulting in clinical improvement in MCTD has been described in case reports [18]. However, use of TNF blockade in the management of MCTD should be undertaken with caution and close monitoring.

Raynaud's phenomenon

Raynaud's phenomenon is present in over 80% of those with MCTD. It is present early in MCTD, and is largely unresponsive to low-dose corticosteroid therapy. The goals of therapy are to reduce the frequency and severity of attacks and to prevent the formation of digital ulcerations. Avoidance of cold stimuli or sudden temperature changes is thought to be key. In smokers, prompt cessation should be encouraged. Medication-based management has traditionally involved the use of calcium channel blockers, particularly those with prominent peripheral vasodilatory effects such as nifedipine. A meta-analysis of the clinical efficacy of calcium channel blockers in primary Raynaud's concluded that there was likely a small beneficial effect with an estimated reduction of between 2.8 and five episodes per week, and a 33% reduction in severity [19]. A similar meta-analysis in Raynaud's in patients with systemic sclerosis concluded that there was a moderate benefit, with an estimated reduction of 8.3 episodes every 2 weeks and a 35% reduction in severity [20]. Thus, the efficacy of these agents seems limited.

α -1 antagonist vasodilators have been used for Raynaud's phenomenon. A selective α (2C)-adren-ergic receptor antagonist demonstrated clinical efficacy in recovery from vasospasm induced by cold exposure in patients with systemic sclerosis in a single-center, placebo-controlled, crossover clinical trial [21]. Parenteral prostacyclin analogs, such as iloprost, have been used with success in patients with severe Raynaud's secondary to systemic sclerosis. In one study, the average daily duration of attacks, average duration of a single attack and the number of attacks was reduced by iloprost therapy [22]. However, oral iloprost at 50 mg twice daily did not demonstrate clinical efficacy in a randomized, controlled study [23].

There is less evidence for other interventions, such as the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. A recent, randomized, double-blind, placebo-controlled trial of the agent quinapril at 80 mg/day for 2–3 years in a population of patients with systemic sclerosis with limited cutaneous involvement did not have significant effects on the frequency or severity of episodes of Raynaud's phenomenon, and did not alter the number of new ischemic ulcers appearing in the hands – the primary outcome measure [24].

One controlled study touted the efficacy of fluoxetine in both primary and secondary Raynaud's phenomenon [25]. Sildenafil, a phosphodiesterase inhibitor used for erectile dysfunction, has been shown to be effective at a dose of 50 mg twice daily in at least one study of patients refractory to vasodilator therapy [26].

More severe cases of Raynaud's in MCTD can result in ischemic digital ulcers. The endothelin-1 receptor inhibitor bosentan has been shown to reduce formation of new digital ulcerations by 48% in patients with systemic sclerosis in one study [27]. Parenteral prostacyclin analogs have been used as therapy in this setting as well. A high rate of injection site reactions was reported in one trial of subcutaneous treprostinil [28]. There was a report of improvement in a patient on sildenafil [29].

For mild cases of MCTD, nonpharmacologic therapy would seem to be the first choice, including protection from exposure to cold, avoidance of cigarette smoke and skin protection. In more severe cases, a trial of pharmacologic therapy may be warranted.

Swollen hands

Swollen or 'puffy' hands are often seen as an early manifestation of MCTD [30]. These can sometimes have a 'sausage-like' appearance. It can be one of the presenting manifestations in almost half the patients with MCTD. Eventually, approximately two-thirds of patients develop swollen hands. As with inflammatory arthritis, NSAIDs and/or low-dose corticosteroids can offer symptomatic relief.

Myositis/myalgia

Myositis in MCTD is usually less severe than that seen in most dermatomyositis and polymyositis patients. Some have suggested that the pathogenic mechanisms at work may be distinct with features of both polymyositis and dermatomyositis [31]. When sought, evidence of mild

myositis, with modest elevation of CK in the absence of clinical finding, is common in MCTD [3]. Some patients have mild myalgias and/or weakness. In rare cases, patients have more severe involvement typical of polymyositis or dermatomyositis. The management is similar, with corticosteroids being the mainstay of therapy [32]. Often, patients will have flares that are of lesser clinical severity than those typical of dermatomyositis or polymyositis. In such cases, doses of 0.5 mg/kg/day can be initiated. Significant inflammatory muscle disease can occur and it should be initially treated, as in dermatomyositis and polymyositis, with high-dose corticosteroids (prednisolone 1 mg/kg/day), and after 4–6 weeks tapered if control has been achieved. For those requiring long-term therapy, azathioprine or methotrexate can be corticosteroid-sparing agents. Intravenous immunoglobulins, mycophenolate mofetil or anti-CD20 may be considered in patients with refractory disease.

High-dose intravenous immunoglobulins have been used for the treatment of dermatomyositis and polymyositis refractory to corticosteroids, and are therefore an alternative in managing a patient with active severe or refractory muscle inflammation in MCTD [33,34]. However, they have not been found to be as effective when used as initial therapy [35].

Newer immunosuppressive agents have recently been tested in open-label trials in patients with inflammatory myopathies. Mycophenolate mofetil demonstrated some efficacy in an open study of six patients refractory to prior therapies, including other immunosuppressive agents [36]. Follow-up was for a mean of 22.3 months, and the mean dose was 1.6 mg/day with mean creatine kinase levels decreasing from 2395 to 746.6 IU/l.

Rituximab, a chimeric anti-CD 20 monoclonal antibody that depletes B lymphocytes, has been approved for the treatment of RA [37]. There have been reports of benefit in hematologic manifestations of SLE, including thrombotic thrombocytopenic purpura and immune thrombocytopenia [38]. Clinical trials are underway in SLE, and open-label Phase I/II studies have been published [39]. Rituximab was tested in an open-label eight-patient trial of dermatomyositis, and showed only modest effects in control of muscle disease [40].

Gastroesophageal reflux

The most common abdominal problem in MCTD is abnormal motility of the upper gastrointestinal tract [41,42]. Gastroesophageal

reflux is common in patients with MCTD. The treatment generally follows that of gastroesophageal reflux in systemic sclerosis. Proton-pump inhibitors can be very effective in improving reflux symptoms in patients with connective tissue diseases [43], while histamine receptor 2 blockers and other conservative approaches are clearly much less effective or ineffective in most patients.

Sicca symptoms

Sicca symptoms are present in as many as a third to half of patients with MCTD in published cohorts [44]. As with those with primary Sjogren's syndrome (SS), close ophthalmological and dental follow-up is of utmost importance. Artificial tear preparations are quite useful for the management of dry eyes. Parasympathomimetics such as pilocarpine or cevimeline can be used for symptomatic relief as in primary SS [45]. Immunosuppressive agents have been investigated in SS in an attempt to reduce the glandular infiltration by lymphocytes and, thus, disease manifestations and progression. Topical preparation can help in improving symptoms due to external ocular inflammation. In a study of 38 patients with primary Sjogren's, topical ciclosporin and topical corticosteroid preparations improved ocular symptoms and signs, but did not increase tear production as measured by Schirmer score or rose bengal staining [46].

Hydroxychloroquine has been used in patients with SS in the hope of obtaining both symptomatic relief and disease modification through immunosuppression. In a retrospective, open-label study of 50 consecutive patients with primary SS with mean follow-up of 3 years, improvement was reported in painful eyes and mouth, arthralgias and myalgias.

A recent 6-month, open-label trial of mycophenolate sodium at up to 1440 mg/day in 11 patients with primary SS failed to show significant improvement in objective measures of salivary or tear production. However, there were subjective improvements in patient visual analog scale measurements of ocular dryness and a reduced need for artificial tear supplements [47]. Only modest effects on sicca symptoms were observed in a Phase II trial of leflunomide 20 mg/day in primary SS [48].

Anti-TNF therapy has failed to show efficacy in SS. A 12-week, placebo-controlled trial of etanercept 25 mg subcutaneously twice per week did not show significant clinical benefit in primary SS [49]. Minor salivary gland biopsies

were unaltered by the treatment. A subsequent publication reported that IFN- α pathway activation was present in this cohort at baseline when compared with healthy controls, and was exacerbated in those randomized to treatment with etanercept, perhaps explaining the lack of efficacy of TNF blockade in this population [50]. A randomized, placebo-controlled trial of 103 patients treated with infliximab could not demonstrate clinical efficacy in primary SS [51].

An uncontrolled, 16-patient study with low-dose rituximab (375 mg/m² at weeks 0 and 1) showed some clinical benefit at week 36, with a statistically significant improvement in dryness, fatigue, tender joint count and tender point count by visual analog scale, and in quality of life as evaluated by SF-36. These findings await confirmation in randomized, controlled trials [52].

All patients with dry eye symptoms should have at least annual eye examinations by an ophthalmologist experienced with autoimmune disease and antimalarials. Attention to findings of sicca is important. Similarly, routine dental care is important for those with sicca, as this can lead to an increase in caries and periodontal disease.

Fibromyalgia

The management of generalized articular and muscular aches and its often accompanying fatigue can be challenging for both physician and patient. Care should be taken to differentiate symptoms related to MCTD from those of a secondary pain syndrome, such as fibromyalgia, that would call for a significantly different treatment approach.

The treatment of fibromyalgia has typically involved a combination of both nonpharmacologic and pharmacologic approaches tailored to the individual patient. Typical management plans involve regular physical activity/aerobic exercise, such as walking or swimming, improving sleep habits, managing depression and/or anxiety if present and medication-based therapy for pain.

Medications potentially helpful in improving the pain from fibromyalgia include tricyclic antidepressants such as amitriptyline and muscle relaxants such as cyclobenzaprine. These drugs may also be helpful in improving sleep habits if taken at bedtime. In one meta-analysis, patients taking cyclobenzaprine for their fibromyalgia were three-times as likely to report overall improvement in their symptoms, and to report at least moderate reduction in individual symptoms such as difficulty sleeping [53]. Pregabalin is the first

medication to be approved by the US FDA in the USA for the management of fibromyalgia. Pregabalin at 300, 450 and 600 mg/day significantly increased assessment of sleep improvement and patients' global impressions of fibromyalgia improvement [54]. Gabapentin has been demonstrated to reduce pain in fibromyalgia at doses between 1200 mg/day and 2400 mg/day [55].

Combination therapy has been used in fibromyalgia. Amitriptyline (25 mg/day) and fluoxetine (20 mg/day) each led to significant reductions in pain, global well-being and sleep disturbances as monotherapy, but superior efficacy was observed when used in combination over 4–6 weeks in one crossover trial [56].

Sexual dysfunction

Quality of life issues should be given due attention. The effect of sexual dysfunction in particular can be quite devastating [57]. In a case–control study, the prevalence of erectile dysfunction has been estimated to be 81% in systemic sclerosis and 48% in RA. It appeared to occur on average 3 years after diagnosis in both groups [58]. The clinical efficacy of the phosphodiesterase 5 inhibitors has been studied in patients with systemic sclerosis. Tadalafil 10 mg daily was found to significantly improve erectile function in a 12-week open-label trial of 14 patients with systemic sclerosis [59].

Neurological manifestations

Peripheral neuropathies can be a relatively common manifestation of MCTD, similar to SLE and SS [60]. In a study of 62 patients with primary SS, 27% were clinically diagnosed as having a peripheral neuropathy, and 55% had nerve conduction study abnormalities [61]. Of the total number of patients in the cohort, 13% had a sensory neuropathy, 11% a sensory-motor neuropathy and 31% a motor neuropathy. Gabapentin and pregabalin have led to symptomatic improvement of these neuropathies in patients with MCTD, as have transcutaneous electrical nerve stimulator units [Robert W Hoffman, University of Miami, FL, USA. Pers. Observ.].

There have also been rare reports of transverse myelitis [62] and of optic neuropathy [63] in MCTD. Transverse myelitis has been reported to respond in some cases to high-dose corticosteroid therapy followed by maintenance with azathioprine.

Serositis

Serosal involvement, usually as pleuritis and/or pericarditis, has been well described in various populations with MCTD, including midwestern

Caucasian and Hispanic cohorts [3,13]. It can occur in approximately a fifth of patients as a component of the initial presentation, and has been reported to occur in over 40% of patients cumulatively. In a cohort of 310 patients with SLE from Hong Kong, retrospective review yielded a 12% prevalence of serositis. A total of 69 episodes of serositis were identified in 37 patients. Of these, 26% were episodes of pericarditis/pericardial effusion, 44% were pleuritis/pleural effusion and 30% were peritonitis/ascites. Although NSAIDs were initially administered in 35% of cases, prednisolone was required in 76% of cases. All episodes resolved completely within 2 months [64]. Over a mean follow-up observation of 46 months, nine patients had 18 recurrent episodes. These were again responsive to either NSAIDs or corticosteroid therapy.

As in SLE, patients with MCTD can present with serosal manifestations such as pericardial effusions and even tamponade [65]. These manifestations are usually quite sensitive to moderate- to high-dose corticosteroid therapy (0.5–1 mg/kg/day of prednisone or equivalent).

Pulmonary hypertension

Due to its role as the principal cause of mortality in MCTD, and with the advent of increasingly varied and effective therapies for pulmonary hypertension, early recognition of this clinical feature has gained relevance. Its prevalence has been estimated at 20–25% in MCTD [66]. Although the precise mechanism for pulmonary arterial hypertension (PAH) in MCTD has not been elucidated, a Japanese group reported on upregulation of adhesion molecules ICAM-1 and ELAM-1 and class II MHC molecules on pulmonary artery endothelial cells mediated by anti-U1-RNP IgG or anti-U1-RNP Fab fragments from patients with MCTD [67].

Often, patients with MCTD are not screened for PAH. In one study of community-based rheumatologic practices, only 122 out of 791 patients with scleroderma and mixed connective tissue disease had been studied for PAH. Upon Doppler echocardiographic evaluation of the 669 patients that had never been studied for PAH, 89 (13.3%) had estimated right ventricular systolic pressure greater than or equal to 40 mmHg [68]. A total of 83 of the patients that had never been studied had MCTD, and of these seven were found to have PAH.

A Japanese study of 555 MCTD patients, 83 with MCTD-linked pulmonary hypertension, proposed that the presence of four of six clinical criteria had over 90% sensitivity and specificity

for diagnosis of pulmonary hypertension. The six criteria were: exertional dyspnea, systolic pulsation of the left sternal border, accentuated second pulmonary sound, dilatation of the pulmonary artery on chest radiograph, right ventricular hypertrophy on electrocardiogram and right ventricular enlargement on echocardiogram. The American College of Chest Physicians have issued evidence-based guidelines recommending the screening of asymptomatic patients at high risk for PAH [69]. Echocardiogram with right-sided pressure measurement is a key tool in screening patients for pulmonary hypertension. Positive echocardiographic findings should be confirmed through right heart catheterization [70]. Given the recent developments in the management of PAH, routine screening of these patients should include both 2D echocardiography and also pulmonary function tests, as isolated decreases of the diffusing capacity of the lung for carbon monoxide (DLCO) have been useful markers for PAH.

The initial therapy used for the management of PAH has been immunosuppressive therapy to control underlying inflammation, and vasodilatory therapy. In a French study, 28 consecutive patients with connective tissue disease-related PAH were treated with immunosuppressive agents [71]. No vasodilator agents were added. The immunosuppressive agent utilized was monthly intravenous cyclophosphamide at 600 mg/m² for at least 3 months, with 22 of the 28 patients also receiving systemic corticosteroids. Overall, 29% had achieved a predefined response, which included achieving New York Heart Association (NYHA) functional class I or II with sustained hemodynamic improvement. For the subgroup with MCTD, three out of eight patients responded. For the subgroup with SLE, five out of 12 patients responded. No patients with scleroderma responded.

In another recent publication patients received either immunosuppressive therapy or immunosuppressive therapy in combination with vasodilator therapy, in 23 consecutive patients with PAH associated with SLE and with MCTD at their center [72]. The patients included 16 receiving immunosuppressive therapy, including cyclophosphamide, and seven receiving a combination of immunosuppressives and pulmonary vasodilators, with response to therapy defined as those achieving NYHA functional class I or II with hemodynamic improvement after the last pulse of cyclophosphamide. A total of 50% of those on immunosuppressive therapy alone achieved a response. They also

improved significantly in terms of NYHA functional class, 6-min walking distance and mean pulmonary artery pressure. Of the eight non-responders, six responded to subsequent therapy with vasodilators. A total of 57.1% of those on combination therapy, including vasodilators, responded. Overall, those that had baseline NYHA functional class I or II and/or a cardiac index greater than 3.1 l/min/m² were more likely to respond, suggesting an important role for immunosuppression in early/milder disease.

For many years, calcium channel blockers were the initial choice for vasodilator therapy. Over the past few years, many novel agents have been approved by the FDA for the management of primary pulmonary hypertension. These include prostacyclin analogs and endothelin-1 receptor antagonists. In addition, there has been some interest in the use of phosphodiesterase inhibitors, originally approved for use in erectile dysfunction, for PAH.

Endothelin is a potent vasoconstrictor and smooth muscle mitogen. One of the new agents, bosentan, is an orally bioavailable endothelin-1 receptor antagonist. It is dosed twice daily and has been used with success as monotherapy in both idiopathic PAH and PAH secondary to connective tissue diseases. It significantly improved the primary end point of 6-min walk distance, and the secondary end point of improvement in WHO functional class at 16 weeks [73].

An Italian group recently published their 2-year experience with bosentan in a group of patients with PAH secondary to collagen vascular disease. After reporting initial improvement in exercise capacity and pulmonary arterial pressures in their 12-month report [74], the second-year data showed sustained improvement in right ventricular systolic pressures for the 24 months compared with baseline, but pulmonary artery mean pressure remained unchanged and 6-min walk distances improved in the first year but deteriorated in the second with bosentan single-drug therapy [75].

The phosphodiesterase-5 inhibitor sildenafil has been used as single therapy and in combination therapy for PAH. Proposed mechanisms of action include vasodilation of the pulmonary vasculature and antiproliferative effects. In total, 278 patients with PAH were randomized to oral sildenafil 20, 40 or 80 mg three-times daily or placebo for 12 weeks. A subgroup analysis of the patients with PAH secondary to connective tissue disease was subsequently published [76]. This group

included patients with systemic sclerosis (45%), SLE (23%) and 32% were classified as 'other'. The mean increase in 6-min walk distance was 42 m for 20 mg, 36 m for 40 mg and 15 m for 80 mg, while those on placebo had a mean decrease of 13 m. Improvement in one WHO functional class occurred in 29–42% of patients on active treatment, versus 5% on placebo. Significant improvements were seen in mean pulmonary arterial pressure and pulmonary vascular resistance.

Combinations of these agents have been tested, with sildenafil added to baseline bosentan in one study. Although the subgroup of patients with idiopathic PAH further improved their 6-min walk distance and NYHA class after the addition of sildenafil, the subgroup with PAH secondary to collagen vascular disease failed to show additive improvement [77]. Recently, sequential use of these agents in PAH secondary to collagen vascular disease has been tested in a case series with initial use of sildenafil followed by bosentan therapy [78]. Sildenafil resulted in clinical improvement in 6-min walk distances that were sustained for 6 months, and then further sustained for an additional 6 months on bosentan monotherapy.

Combinations of these agents for PAH have been tested. One early trial of bosentan was added to patients on epoprostenol (intravenous prostacyclin analog) therapy. No significant additive benefit was reported [79]. In a subsequent study, inhaled iloprost was added to patients with idiopathic and secondary PAH on bosentan. At 12 weeks, 6-min walk distances improved by 30 m in the treatment group, a statistically significant change. In total, 34% of the patients in the treatment group improved by one NYHA functional class [80]. Treprostinil, an inhaled prostacyclin analog, was added to bosentan in 12 patients with idiopathic PAH. Further decreases in mean pulmonary arterial pressure (10%) and in pulmonary vascular resistance (26%) were noted at 12 weeks following the addition of treprostinil [81]. There was also a significant improvement in 6-min walk distances.

Interstitial lung disease

Although usually less identified as a cause of morbidity and mortality in MCTD than PAH, interstitial lung disease (ILD) in the form of a fibrosing alveolitis has been identified in over 50% of patients with MCTD [82]. In one series incorporating 41 Japanese patients with MCTD and abnormal findings on high-resolution CT,

the most common pulmonary findings were ground glass attenuation, nonseptal linear opacities and peripheral and lower lobe predominance [83].

Clinical workup in MCTD should include assessment for possible ILD with pulmonary function tests and high-resolution CT. The presence of 'ground-glass' infiltrates on high-resolution CT is highly suggestive for the presence of inflammatory interstitial lung disease. Medication-based management is similar to that for interstitial lung disease in SLE and systemic sclerosis, and initially includes oral corticosteroids at 1 mg/kg/day of prednisolone or equivalent. Cyclophosphamide in monthly intravenous pulses or orally (1–2 mg/kg/day) is then added and the corticosteroids gradually tapered.

An Italian group screened patients with different connective tissue diseases for ILD [84]. In this mixed group, 69 out of 81 patients (85.1%) had some evidence of ILD by high-resolution CT. Pulmonary function test and/or plain radiograph abnormalities occurred in only 40.7% of the patients. In 35 patients the predominant abnormality was inflammatory findings such as 'ground glass', and in 34 patients there were mostly fibrotic findings.

In one series, 144 consecutive patients with MCTD were formally studied for ILD with high resolution CT. In total, 96 out of 144 (66.7%) had evidence of active ILD. A total of 75 patients had 'ground glass' infiltrates suggestive of active pulmonary inflammation, and 21 had both ground glass and evidence of fibrosis [85]. All patients were then treated, with 45 receiving prednisolone at 2 mg/kg/day for 6–8 weeks and 51 receiving prednisolone plus oral cyclophosphamide at 2 mg/kg/day. Repeat high-resolution CT 6 months later revealed resolution of ground glass in 67 out of 96 patients (69.8%). Ground glass with mild fibrosis was noted in 15 patients, and fibrosis in 13 patients.

Early data from patients with systemic sclerosis suggest potential efficacy of mycophenolate mofetil in the management of interstitial lung disease, with statistically significant improvement in DLCO in an open-label study of five consecutive patients with systemic sclerosis and recent onset alveolitis by high-resolution CT [86]. Further investigation of this potential option is needed.

Conclusion

Mixed connective tissue disease is widely recognized as a distinct entity, with characteristic clinical, genetic and immunologic features. While

the prevalence of some is clearly higher than others, the particular clinical presentation is distinctive in each patient and, thus, the treatment should be tailored to the individual patient.

The medication-based interventions used for MCTD have typically not been demonstrated to be effective in controlled clinical trials designed for these patients. Rather, most of these treatments are directed at specific clinical features and are taken from the clinical trial and clinical report experience in the treatment of those specific features in other rheumatic diseases such as SLE, systemic sclerosis, dermatomyositis and SS. Notable recent therapeutic advances have resulted in the evolution of therapy for several clinical features of MCTD, but in particular that of PAH.

Future perspective

Over the next decade, research in MCTD should continue to evolve with better descriptive work in populations of different ethnic backgrounds.

It is hoped that subsets of patients with differing combinations of clinical manifestations will be better characterized, perhaps even in terms of response to particular therapies through genetic studies and/or pharmacogenomics. The management of MCTD will also continue to evolve as new and superior medication-based interventions are developed for manifestations such as Raynaud's phenomenon, arthritis, pulmonary fibrosis and PAH.

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Executive summary

- Mixed connective tissue disease (MCTD) is a distinct clinical entity with a unique combination of clinical features and a novel autoantibody directed against U1-ribonucleoprotein.
- Criteria for classification of MCTD have been developed and published.
- Particular attention should be given to early recognition of pulmonary involvement.
- Pulmonary arterial hypertension is the principal cause of mortality in MCTD.
- The management of MCTD has developed from treatments used in other connective tissue diseases, in particular, systemic lupus erythematosus, systemic sclerosis and dermatomyositis.
- The therapeutic plan needs to be tailored to the specific clinical manifestations present in each patient.
- Antimalarials, NSAIDs and low-dose corticosteroids can effectively relieve articular manifestations.
- High-dose corticosteroids may be necessary to control myositis and to control moderate-to-severe serosal manifestations.
- Corticosteroid-sparing agents such as methotrexate and azathioprine may be necessary in those that require chronic moderate or high corticosteroids for adequate disease control.
- The treatment options for pulmonary arterial hypertension now include, in addition to calcium channel blockers, prostacyclin analogs, phosphodiesterase-5 inhibitors such as sildenafil and endothelin-1 receptor antagonists such as bosentan. Combinations of these agents have also been investigated.

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