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Treatment of Mixed Connective Tissue Disease

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The term mixed connective tissue disease (MCTD) was coined by Sharp and colleagues [1] in 1972 to describe a group of patients who had overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma, and polymyositis (PM). MCTD was considered to be distinct because all of these patients exhibited high titers of autoantibodies to a ribonuclease-sensitive component of extractable nuclear antigen [1], later identified as U1 ribonucleoprotein (RNP) [2,3]. Initial descriptions of this syndrome emphasized a good prognosis with an excellent response to corticosteroid therapy and the absence of significant renal or central nervous system involvement [1,4]; however, subsequent studies with longer periods of observations have shown that MCTD is not invariably benign, accompanying organ involvement may be significant, and some clinical manifestations are not responsive to steroids [5–9]. Furthermore, poor prognosis has been associated with pulmonary hypertension, which occurs in certain subsets of patients who have MCTD and causes significant morbidity and mortality [5,9]. Pulmonary hypertension represents the most common disease-related cause of death in MCTD and may be an important target for early aggressive treatment.

Historical perspective on treatment of mixed connective tissue disease

In the initial report by Sharp and colleagues [1], MCTD seemed to be responsive to corticosteroid therapy with a favorable prognosis over a short-term observational period (2 months to 8 years). Of the 25 original patients, 21 who had ‘‘major organ involvement’’ were treated with corticosteroids (usual starting

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dosage of prednisone, 1 mg/kg) and 7 also received an alkylating agent. All responded favorably with improvement in myositis, serositis, arthritis, lymphadenopathy, hepatosplenomegaly, fever, anemia, and leukopenia. Some even had improvement in their skin swelling and thickening. More than 70% of treated patients received only one course of high-dose corticosteroids (prednisone, 1 mg/kg) with significant improvement in their clinical manifestations. The remaining 28% required repeated courses for recurrent or persistently active disease. At the end of the follow-up period, all 25 patients were alive and nearly all had a favorable response to steroids; 7 were off therapy, 10 were receiving prednisone at 10 mg or less daily, and only 4 were on prednisone at more than 10 mg/d [1].

Subsequent long-term follow-up studies [5–9], however, have not supported Sharp and colleagues' initial optimistic outlook on MCTD. In particular, extended observations have revealed that not all patients who have MCTD have a benign clinical course and that not all clinical features are steroid responsive. These observations were documented first in the follow-up report of the original 25 patients by Nimelstein and colleagues [8]. In 22 patients who were available for review, inflammatory manifestations (ie, arthritis, serositis, fever, myositis, and skin rash) had improved significantly following corticosteroid treatment, whereas sclerodermatous features (ie, Raynaud's phenomenon [RP], sclerodactyly, esophageal disease, sclerodermatous bowel disease, and chronic pulmonary interstitial disease) persisted and often were unresponsive to therapy. Additionally, 8 patients had died. At least 2 of the deaths could have been attributed to an underlying rheumatic process or a complication related to its treatment. One died of scleroderma-like renal crisis, whereas the other died of respiratory infection while receiving immunosuppression for renal involvement. Although many surviving patients did well and were off therapy or required only low-dose maintenance steroids, overall mortality was high in this group (36%) and sclerodermatous features were persistent and often refractory to treatment.

Several longitudinal studies of patients who have MCTD and anti–U1-RNP antibodies have since been published and confirmed the variable clinical course and prognosis in MCTD; it ranges from benign self-limited disease with little or no steroid requirements to a severe progressive course that is characterized by proliferative vasculopathy with pulmonary hypertension and increased mortality [5–10]. In the most recent longitudinal study of 47 patients who had MCTD who were followed for a mean of 15 years, 17 (36%) were in remission (prednisone <6 mg/d and no cytotoxic drug therapy) following treatment with corticosteroids of varying doses (low, moderate, or high) with ($n = 9$) or without ($n = 8$) cyclophosphamide ($\geq$ 50 mg/d); 12 (26%) were improved but still receiving prednisone at less than 20 mg/d; and 18 (38%) responded less favorably to treatment (7 [15%] had persistently active disease, despite aggressive immunosuppression and 11 [23%] had died) [5]. In general, inflammatory manifestations markedly improved with treatment in these patients, whereas sclerodactyly, pulmonary involvement, and nervous system disease tended to persist [5].