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Cyclophosphamide for Scleroderma Lung Disease

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Clinically significant interstitial lung disease affects patients with systemic sclerosis (scleroderma) and is a cause of morbidity and mortality in approximately 40 percent of these patients.¹ Management of this condition remains difficult and controversial.^{2,3} In this issue of the *Journal*, Tashkin and colleagues⁴ report the results of a multicenter, placebo-controlled trial of oral cyclophosphamide in patients with well-defined, symptomatic scleroderma-related interstitial lung disease and alveolitis. They document small but statistically significant improvements in lung function and symptoms with cyclophosphamide administered over the course of one year — the first positive results of a placebo-controlled trial in this field.

How should these results be translated into clinical care? In this trial, a change in the expected annual decline in the forced vital capacity (FVC, expressed as a percentage of the predicted value) was the primary end point. Although the dropout rate was higher than anticipated (approximately 33 percent of the patients did not complete one year of cyclophosphamide therapy), the statistical analysis allowed the calculation of longitudinal changes in the FVC in the majority of the patients. This analysis showed an adjusted difference of 2.53 percent in the FVC favoring cyclophosphamide ($P=0.03$). This modest difference was less than that anticipated by the investigators — a 9 percent annual decline in the FVC, as derived from published case series. In the majority of the patients in the two study groups, the change in the predicted value of the FVC was less than 5 percent, which is close to the expected natural variability in the percentage of the predicted FVC.⁵ In contrast, no significant treatment-related difference was noted in the diffusing capacity for carbon monoxide, a measure that is considered by some to be a better longitudinal marker of disease progression than the change in the FVC.^{2,6} The explanation of this modest effect remains conjectural, but the size of the effect may reflect the patient population studied.

Previous investigators have suggested that progressive scleroderma-related interstitial lung disease is more likely to develop in patients with low pulmonary function at presentation or rapid disease progression during the first five years after the onset of the first scleroderma-related symptom.⁷ In the patients in the current trial, the duration of the symptoms was longer and the physiological deficits fewer than in patients included in a previous case series that showed a more robust physiological effect of cyclophosphamide therapy.⁸ In this trial, greater improvement with cyclophosphamide was observed in patients with more fibrotic abnormalities at baseline on high-resolution computed tomography than among those with fewer fibrotic abnormalities. These data provide a hint regarding which patients with scleroderma-related interstitial lung disease may be good candidates for treatment with cyclophosphamide.

A beneficial effect of cyclophosphamide therapy was also supported by several statistically significant differences in the secondary end points, even though these differences were also small. Changes in scores for skin thickness favored cyclophosphamide, although the magnitude of the change in the scores was limited, as compared with the inherent variability of this outcome measure.⁹ In addition, changes in the severity of dyspnea, as assessed according to the transitional dyspnea index, favored cyclophosphamide. Given that the transitional dyspnea index was administered by nurse coordinators with access to other information, which could introduce a bias, and the limited validation of this index in interstitial lung disease, the results regarding dyspnea should be interpreted with caution.

An important consideration when interpreting these limited therapeutic benefits of treatment with cyclophosphamide is the need for a thorough assessment of the risks of the drug, arguably the most toxic immunosuppressive agent currently used to treat autoimmune diseases. The duration

of follow-up in this study was insufficient to assess the effect of cyclophosphamide on survival or on the incidence of secondary malignant diseases. When cyclophosphamide is used as an immunosuppressive agent in the treatment of other rheumatologic diseases, the risks of cancer and gonadal failure increase with cumulative doses and are greater when the drug is administered daily, rather than as an intermittent monthly bolus. Daily cyclophosphamide results in higher cumulative doses than do monthly boluses when both are administered for the same duration. For example, one year of oral cyclophosphamide at a daily dose of 2 mg per kilogram of body weight for scleroderma-related interstitial lung disease would expose a patient weighing 75 kg (165 lb) to a dose of 55 g, as compared with exposure to 9 g after six pulses of intermittent monthly boluses for lupus nephritis. Cumulative doses of 30 to 100 g of cyclophosphamide are associated with a substantially greater risk than are lower doses.

In two long-term follow-up studies, the incidences of malignant conditions, including bladder, hematologic, and skin cancers, in patients with rheumatoid arthritis treated with cyclophosphamide, as compared with age-matched control patients with rheumatoid arthritis, were 24 percent and 13 percent,¹⁰ respectively, and 18.5 percent and 5 percent,¹¹ respectively. Differences in the incidence of cancers began to emerge after five to seven years of treatment.¹²

Daily cyclophosphamide increases the risk of hemorrhagic cystitis (reported in 5 to 34 percent of treated patients),¹³ bladder fibrosis, and transitional-cell carcinomas of the urinary tract; bladder cancers continue to develop for at least 20 years after exposure.¹²⁻¹⁴ Hematologic cancers are usually associated with large cumulative doses of cyclophosphamide (between 80 and 120 g).¹⁵ In contrast, premalignant changes related to infection with the human papillomavirus appear earlier during treatment; these changes appear among patients with systemic lupus erythematosus treated with intermittent monthly boluses of cyclophosphamide during the first three years of treatment in 4 percent to 34 percent.¹⁶

Gonadal failure is also a major potential toxic effect of cyclophosphamide. In patients with breast cancer, the mean cumulative dose of cyclophosphamide required to produce gonadal failure in women in their 20s, 30s, and 40s were 20 g, 10 g,

and 5 g, respectively — doses far lower than the cumulative doses in the current study.¹² On the basis of the description, the daily cyclophosphamide regimen in this study would produce cumulative doses ranging from 20 to 70 g. Thus, the risk of gonadal failure would be high among women of all ages: cervical cancer and bladder cancer would be expected to increase among those receiving doses within this range, with a smaller increase in the risk of myelodysplastic syndromes and lymphomas. On one hand, Tashkin and colleagues document the expected, acute hematologic toxic effects of cyclophosphamide, but they do not document a differential number of serious adverse events. On the other hand, cyclophosphamide was associated with an increase in the number of cases of pneumonia and a greater number of patients withdrawing from therapy early in the study, as compared with placebo. Furthermore, despite the relatively short follow-up period, three malignant diseases were identified in the cyclophosphamide group.

In conclusion, this well-designed trial will be regarded as a sentinel study confirming a beneficial response to cyclophosphamide in highly selected patients with scleroderma-related interstitial lung disease. In the absence of long-term follow-up data on mortality and the development of malignant diseases, however, the modest therapeutic response and the potential for significant toxic effects do not, in our opinion, support the conclusion that one year of daily cyclophosphamide should be considered routine therapy for all such patients. Additional analyses based on the current data set could offer further guidance regarding patients who are most likely to benefit from this drug. Future studies will be required to provide additional information and build on the encouraging, albeit preliminary, results reported by Tashkin and colleagues.

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Autoantibodies against PDGF Receptor in Scleroderma

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Scleroderma (systemic sclerosis) is characterized by the deposition and accumulation of excessive amounts of collagen and extracellular-matrix molecules, the dysfunction of microvascular endothelial cells, and altered immune tolerance. These interacting and interdependent processes lead to chronic inflammation and tissue fibrosis.

To investigate complex mechanisms of disease pathogenesis, conventional wisdom dictates that a single aspect of disease be dissected out and examined in detail. The skin is a prominent target organ in scleroderma, and fibroblasts from affected patients are activated and display a variety of properties, including increased production of collagens and other extracellular-matrix proteins, abnormal growth patterns, and resistance to apoptosis. Unfortunately, such fibroblasts gradually lose their activated properties in culture. This phenomenon is an example of what systems biologists refer to as an "emergent property." Although such fibroblasts have a measurable, inherent biologic abnormality, the characteristics or emergent properties of these cells cannot be fully appreciated when they are isolated from other components that interact together in vivo with a resultant phenotype that is more complex than the sum of the individual parts.

What factors sustain the fibroblast phenotype in vivo in scleroderma? At the earliest stages, small-vessel abnormalities and lymphocyte activation and infiltration of target organs are present before the appearance of clinically apparent fibrosis. Thus, the sustaining factors include endothelial cells, fastidious subpopulations of aberrant fibroblasts or their precursors, and immune-system cells. Svegliati Baroni et al.¹ suggest in this issue of the *Journal* that autoantibodies could be one of the factors that sustain the profibrotic phenotype of such fibroblasts — an effect reminiscent of that of stimulating antibodies on the thyrotropin receptor in causing Graves' disease.

The existence of autoantibodies in scleroderma was described more than 40 years ago. Indeed, such autoantibodies, some highly disease-specific, are present in virtually all patients with scleroderma. Although the important autoantibodies are directed against nuclear components, it is clear that most patients with scleroderma also have antibodies against extracellular-matrix and cell-surface proteins, proteases, fibroblasts, and endothelial cells.² What would be needed to demonstrate that autoantibodies in scleroderma are pathogenic, not just epiphenomena resulting from