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Ribavirin use in humans

To the Editor:

The autoimmune disease of NZB/NZW mice has received considerable investigative attention as an animal model for human systemic lupus erythematosus (SLE). Genetic, viral, and immunologic factors have been implicated in the pathogenesis of this disorder (1–3). Recently, the administration of the antiviral agent ribavirin (I-B-D ribafuranosyl-1,2,4,triazole-3) was reported as capable of retarding the clinical and laboratory manifestations of established autoimmune disease in NZB/NZW mice (4). We therefore studied the effect of ribavirin on human SLE by starting treatment in 3 patients with overt disease.

Patient 1. A white woman who was born in 1944 developed polyarthritis in 1964. Treatment over the years included penicillin, salicylates, and hydroxychloroquine, but the symptoms did not completely subside. In December 1970, Raynaud's phenomenon and alopecia appeared. Antinuclear antibodies and LE preparations were positive. Renal function tests and complement levels were within normal limits. In July 1977, the patient developed fever and polyarthritis involving finger joints, wrists, and knees. Results of routine laboratory work were normal, the antinuclear antibody test, and several LE preparations were positive, and renal function tests produced normal results. Complement levels (CH50, C3, C4) were normal and the urinary sediment was normal except for an occasional granular cast. On August 15, 1977, she was started on ribavirin 30 mg/kg a day for three consecutive weeks. Her major clinical findings at that time were arthralgias, cutaneous rash, and daily proteinuria averaging 3.0 gm a day (range 1.8–4.2) on 5 consecutive determinations. On September 6, 1977, the medication was discontinued and on the 10th of September a complete laboratory evaluation was performed. Her clinical symptoms remained essentially unchanged and her 24-hour proteinuria was 2.9 gm. The patient was then placed on oral steroids (40 mg a day) and at the time of this report is in full remission on 7.5 mg of prednisone a day.

Patient 2. In March 1971, a 31-year-old black woman developed an extensive rash resembling erythema multiforme, but with histologic characteristics of lupus erythematosus. Throughout the next few years, discoid lupus lesions appeared on the scalp and palmar skin, and morning stiffness and arthralgias became prominant. Transient proteinuria was noted in August 1976, leading to her hospital admission. A renal biopsy showed findings consistent with a proliferative glomerulonephritis, LE cell tests were positive, and DNA binding assay (Farr) was 67%. Ribavirin, 30 mg/kg, was started July 15, 1977, and maintained for 3 straight weeks without either clinical or laboratory response. Prednisone was started and resulted in marked clinical response.

Patient 3. A white woman, born in 1939, presented in March 1972 with pallor, weakness, and generalized fatigue. She was promptly admitted to the hospital for diagnostic workup. Admission laboratory work revealed a hematocrit of 25% and a white cell count of 3,800/mm^3. Westergren sedimentation rate was 112

mm. Urinalysis was normal except for hematuria. Her serum creatinine was 3.0 mg% and BUN was 85 mg%. Antinuclear antibody test was positive to a titer of 1:512 (peripheral pattern), and several LE cell preparations were positive. Renal biopsy showed proliferative changes in the glomeruli, and partial hyalinization was present in a few areas. On April 4, 1978, she was started on ribavirin intravenously 10 mg/kg daily for 2 consecutive weeks. On April 20th the patient's clinical and laboratory evaluation was virtually unchanged. Her serum creatinine was 4.3 mg%, hematocrit 27%, BUN 90 mg%, white cell count 4,200/mm^3, C3 30 mg%, C4 12 mg%, and CH50 22 units. On April 10th the patient was started on 60 mg per day of prednisone and after continuous use for 6 consecutive weeks, no significant changes were observed on clinical and laboratory evaluation. At the time of this report her medications includes 30 mg of prednisone and 150 mg of azathioprine.

The similarity between NZB mice and SLE has led to the use of these mice for drug trial before patients are subjected to clinical usage. Ribavirin given to NZB mice with established lupus nephritis was capable of prolonging survival and reducing the titer of antibodies to native DNA. We report herein no benefit on the serologic and clinical abnormalities of patients with SLE when ribavirin was given either by oral or intravenous route. The current data do suggest that, despite the enthusiasm generated by its efficacy in reversing the autoimmune features of NZB/NZW mice, ribavirin may not offer such results in SLE patients, at least for the period and dosages used in the present study.

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Sickled erythrocytes in synovial fluids

To the Editor:

The rheumatologic manifestations of sickle cell anemia play a large role in the morbidity of that condition (1,2). Not surprisingly, sickled erythrocytes have been observed in pathologic synovial fluids from individuals homozygous for hemoglobin (Hb) S (1–3). There is no acceptable evidence that individuals with hemoglobin AS have an increased incidence of hemarthrosis, aseptic necrosis, or other joint disease. There is however, a single reported patient with HbAS in whom sickled erythrocytes were observed in a synovial fluid (2). This patient had an inflammatory arthritis and hemarthrosis. Hemarthrosis was reported in a second patient with sickle trait and chronic inflammatory arthritis, but sickled erythrocytes were not observed (4). I have encountered two patients with chronic arthritis in whom the observation of sickled erythrocytes in synovial fluid was the initial indication of unsuspected hemoglobin AS.

The first patient was a 59-year-old black woman with 10 years of unrecognized tophaceous gout. Aspiration of a mildly warm and swollen knee yielded 20 ml of cloudy, yellow fluid with a high viscosity. A wet preparation of the fluid was examined within 5 minutes of aspiration. The white cell count was 600/mm^3 with 21% mononuclear phagocytes, 50% lymphocytes, and 29% synovial lining cells. The red cell count was 1,200/mm^3 with 20% of the erythrocytes sickled to some degree. Many extracellular urate crystals and cartilage fragments were observed. Her peripheral blood hemoglobin was 12.0 gm/dl, urate was 11.3 mg/dl, and blood urea nitrogen was 36 mg/dl. A sickle cell preparation was positive.

The second patient was a 55-year-old black man with ankylosing spondylitis which included peripheral joint involvement. Complicating medical problems included alcoholism, cirrhosis of the liver, and generalized osteoporosis. He suffered intraarticular fracture of the right knee 3 years earlier. The right knee had post-traumatic deformity and was slightly warm and tender. An atraumatic aspiration yielded 6 ml of slightly bloody fluid. A wet preparation was examined within 15 minutes. The white blood cell count was less than 600/mm^3. Most of the red cells present were crenated and approximately 15% were sickled. No crystals or marrow elements were identified. Subsequent evaluation disclosed 38% HbS and 62% HbA. The peripheral hemoglobin was 9.2 gm/dl, a value compatible with his chronic illness and nutritional state.