CME CREDIT

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The uncertain role of immunosuppressive agents in Sjögren's syndrome

IMMUNOSUPPRESSIVE THERAPY has constituted, for the last 40 years, the cornerstone treatment of systemic autoimmune disorders with major organ involvement. In particular, the use of cyclophosphamide, an alkylating agent, has changed the outcome of Wegener's granulomatosis and has significantly altered the prognosis of lupus nephritis.[1,2]

In this report we present the role, if any, of immunosuppressive agents in the treatment of Sjögren's syndrome.

A PATIENT WITH SJÖGREN'S SYNDROME

A 40-year-old woman was referred to an outpatient clinic because of dry mouth and eyes, nonproductive cough, generalized arthralgias, and malaise of 5 years' duration. She had an atrophic, red, and dry tongue, bilateral parotid gland enlargement, and nonpalpable purpura of the lower extremities.

The Schirmer's eye test (a simple measurement of lacrimal production in which a piece of filter paper is inserted in the lower conjunctival pouch and the amount of wetting is measured; wetting of more than 5 mm in 5 minutes is considered normal) was less than 2 mm in 5 minutes in both eyes, and slit lamp examination after rose bengal staining showed filamentary keratitis.

Laboratory evaluation revealed hypergammaglobulinemia and cryoglobulinemia. Immunoelectrophoresis of the cryoprecipitate demonstrated an IgM-kappa monoclonal protein with rheumatoid factor activity (type II cryoglobulinemia).[3]

ABSTRACT

Although Sjögren's syndrome is an autoimmune disorder, immunosuppressive agents have yielded disappointing results in clinical trials. In this paper we summarize our experience using immunosuppressive and cytotoxic agents to treat Sjögren's syndrome, and present an illustrative case history.

KEY POINTS

Therapy of Sjögren's syndrome remains empirical and symptomatic, aiming mostly to alleviate sicca symptoms (dry mouth and eyes).

Immunosuppressive agents (methotrexate, cyclosporine) may improve the symptoms of Sjögren's syndrome, although they do not alter the decreased lacrimal and salivary flow rates or the histologic markers of the disease. The lack of objective improvement coupled with the potential side effects make the use of these agents problematic.

Alkylating agents, notably cyclophosphamide, significantly increase the risk of lymphoma in patients with Sjögren's syndrome. Therefore, these agents should be reserved for life-threatening disease manifestations.

A PATIENT WITH SJÖGREN'S SYNDROME

■ Other findings were a positive antinuclear antibody titer at 1:1280 dilution (normal: negative at 1:40 dilution), antibodies to Ro/SSA and La/SSB, and a positive rheumatoid factor. The creatinine clearance was 65 mL/minute (normal: 75–115 mL/minute).

A minor salivary gland biopsy revealed the presence of focal lymphocytic infiltrates compatible with the diagnosis of Sjögren's syndrome.[4] Treatment was initiated with tear substitutes and hydroxychloroquine 200 mg daily.

TREATMENT OF GLANDULAR MANIFESTATIONS

Sjögren's syndrome is a common (0.5% of the female population),[5] slowly progressive autoimmune disorder affecting primarily women in the fourth and fifth decade of life. It is characterized by lymphocytic infiltration and destruction of the exocrine glands (predominantly the lacrimal and salivary glands), resulting in dry eyes and mouth.

Symptom relief is the primary goal of Sjögren's syndrome therapy

Despite progress in understanding the pathogenesis of Sjögren's syndrome, therapy remains empiric and symptomatic, primarily aimed at alleviating sicca symptoms with eye lubricants, saliva secretagogues, and substitutes, and at stimulating glandular secretion with systemic therapy. Pilocarpine, a muscarinic-cholinergic agonist, is known to stimulate salivary flow in patients with salivary gland dysfunction. In one study, pilocarpine 5 to 10 mg three times daily relieved the symptoms of xerostomia in patients with Sjögren's syndrome. Only mild and tolerable side effects were observed, most commonly sweating and flushing.[6]

Immunosuppressive agents have been only partially successful in clinical trials

In an attempt to alleviate the symptoms of Sjögren's syndrome by altering the disease process, researchers at the University of Ioannina, the National University of Athens, and Laiko General Hospital in Athens conducted a series of clinical trials over the past decade, testing a number of immunosuppressive agents. Unfortunately, despite some promising results, immunosuppressive therapy proved only partially successful.

Cyclosporine. The lymphocytic infiltration of the labial minor salivary glands in Sjögren's syndrome consists mainly of activated memory helper-T cells.[7] Since cyclosporine acts by inhibiting interleukin-2 (IL-2) production by activated helper-T cells, we wondered if it could be beneficial in treating Sjögren's syndrome. In a double-blind study, cyclosporine (5 mg/kg body weight/day) improved subjective xerostomia and seemed to retard the evolution of the histopathologic lesions of Sjögren's syndrome. However, no changes in the objective indices of lacrimal and parotid flows were observed.

The minimal clinical improvement seen in this study, coupled with the cyclosporine's potential serious side effects (hypertension, nephrotoxicity) make its use questionable in this disease.[8] It is noteworthy, however, that when cyclosporine eye drops were used in a placebo-controlled trial, we observed an improvement of dry eye symptoms and signs (keratoconjunctivitis sicca).[9] This finding indicates that the amount of drug reaching the area of inflammation may be important. On the other hand, the local use of such agents is of limited value for the systemic form of this disease.

Methotrexate. Because there is evidence that proinflammatory cytokines (IL-1, IL-6) are found in histologic lesions in the labial salivary glands of patients with Sjögren's syndrome,[10] and considering that methotrexate is an immunoregulatory and anti-inflammatory agent that suppresses these molecules, we gave methotrexate (3 mg/kg body weight/week) to patients with Sjögren's syndrome in an open trial. This regimen alleviated the subjective symptoms of dry mouth and eyes and decreased the frequency of parotid gland enlargement, dry cough, and purpura, but no alteration was noted in the lacrimal or salivary flow rates.[11] Therefore, although methotrexate is considered safe and appears capable of improving the subjective symptoms of Sjögren's syndrome, the lack of objective improvement in this trial makes its routine use questionable in this disease.

Azathioprine, a well-established immunosuppressive agent, has been used in treating systemic lupus erythematosus and rheumatoid arthritis and for preventing transplant rejection. Low doses of azathioprine (1 mg/kg body weight/day) were given to patients with

Sjögren's syndrome in a double-blind, placebo-controlled trial. No therapeutic benefit was observed in the symptoms, signs, and serologic and histologic markers of the syndrome. Further, a high frequency of side effects was noted, suggesting that azathioprine does not have a role as a disease-modifying agent in Sjögren's syndrome.[12]

Corticosteroids, in our experience, do not alter the natural history of dry mouth and eyes and parotid-gland enlargement and may induce, if used locally, severe corneal lesions. They are reserved for severe extraglandular manifestations affecting the lungs, kidneys, muscles, and blood vessels.

Hydroxychloroquine does not affect the sicca manifestations of Sjögren's syndrome, although it can be beneficial for treating arthralgias or arthritis in patients with this disease.[13]

TREATMENT OF MAJOR ORGAN INVOLVEMENT

In one fourth of patients with Sjögren's syndrome the lymphocytic infiltrates extend beyond the exocrine glands and affect parenchymal organs, resulting in bronchitis sicca, biliary cirrhosis, thyroiditis, chronic pancreatitis, and interstitial nephritis with or without renal tubular acidosis.[14] In a small number of patients, immune–complex-mediated pathology is found, such as glomerulonephritis and vasculitis of small or medium-sized vessels or both.[15,16]

Severe extraglandular disease such as interstitial pneumonitis, glomerulonephritis, vasculitis, and peripheral neuropathy is usually treated with systemic corticosteroids (eg, prednisolone 0.5 to 1 mg/kg body weight/day).

Cyclophosphamide is reserved for serious, resistant cases

In patients with life-threatening manifestations of Sjögren's syndrome, an alkylating agent such as cyclophosphamide may be the drug of last resort.

Alkylating agents substitute alkyl radicals into other molecules, altering the function of proteins and nucleic acids and leading ultimately to cell death. Mechlorethamine (a nitrogen mustard) was the first of the alkylating agents to be used clinically in the treatment of immune-mediated disease (in the successful treatment of a patient with Wegener's granulomatosis in 1954). However, cyclophosphamide has nearly replaced the other nitrogen mustards as the alkylating agent of choice for treating non-neoplastic diseases, as it has the advantages of having less significant toxic side effects than do other alkylating agents while suppressing the immune system more, as demonstrated in studies in animals. The most consistent finding in cyclophosphamide-treated patients is lymphocytopenia of both T and B lymphocytes, with early preferential depletion of B lymphocytes as reflected in the suppression of immunoglobulin production.

Although the clinical toxicity of cyclophosphamide is less severe than that of

Severe extraglandular disease is usually treated with corticosteroids

PATIENT FOLLOW-UP

Six years after the initial diagnosis, an exacerbation of the disease was noted with malaise, arthralgias, muscle weakness, and palpable purpura of the lower extremities. Further evaluation revealed hyperchloremic acidosis, hypokalemia, alkaline urine, and calcium phosphate renal stones. Thus, the patient presented a clinical picture of type I (distal) renal tubular acidosis. A percutaneous needle renal biopsy study revealed interstitial nephritis.

Treatment with hydroxychloroquine was stopped, and prednisolone (0.5 mg/kg body weight/day) and oral supplements of potassium and sodium bicarbonate were started, resulting in improvement of the metabolic aberrations. However, gradual tapering of the prednisolone dose was followed by aggravation of the lower-extremity purpuric lesions, the appearance of malleolar ulcers, recurrent renal colic, and a decrease in creatinine clearance to 45 mL/minute. A biopsy of a skin lesion on the anterior aspect of the shin revealed leukocytoclastic vasculitis.

Although the patient continued to receive prednisolone, her condition deteriorated with malaise, ulcerating purpuric lesions of the lower extremities, a further decrease of the creatinine clearance to 30 mL/min, and hypertension. Treatment with monthly intravenous cyclophosphamide pulses (0.5 g/m^2 body surface) was initiated. This resulted in improvement of the skin lesions and stabilization of renal function. However, the above treatment was discontinued 1 year later because of the development of generalized lymphadenopathy. A lymph node biopsy study revealed a non-Hodgkin's lymphoma.

other nitrogen mustards, caution is advised when the drug is considered for use in rheumatic diseases, not only because of its acute toxic effects (neutropenia, alopecia, nausea and vomiting, mucosal ulcerations, hemorrhagic cystitis) but also because of its propensity for causing cancer and infertility.

Cyclophosphamide is known to increase the risk of lymphoma in Sjögren's syndrome. A study reported in 1978 that patients with Sjögren's syndrome had a risk of developing B-cell lymphoma that was up to 44 times higher than in controls matched for age, sex, and race.[17] Predictive factors for lymphoma are parotid gland enlargement, lymphadenopathy, mixed monoclonal cryoglobulinemia, and previous exposure to cytotoxic agents.[18] In particular, it seems that cytotoxic drug treatment increases the risk of lymphoma in Sjögren's syndrome 100-fold.[15] Therefore, cyclophosphamide treatment in patients with Sjögren's syndrome is reserved for serious systemic manifestations of the disease, such as glomerulonephritis refractory to prednisolone, and systemic necrotizing vasculitis.

Cytotoxic drugs increase risk of lymphoma 100-fold

Treatment of lymphoma in patients with Sjögren's syndrome depends on the histologic type, location, and extension, and follows the rules treating for lymphoma in the general population.

FUTURE DIRECTIONS

Although a definite and systemic cure for Sjögren's syndrome is still unavailable, a lot of research is in progress in order to abrogate the autoimmune reactivity seen in this disease. For example, monoclonal antibodies counteracting the proinflammatory cytokines IL-2 and IL-6 existing in the histologic lesion of Sjögren's syndrome are reasonable agents. Administration of anti-inflammatory cytokines such as transforming growth factor beta or IL-10 could also contribute to Sjögren's syndrome immunointervention.

The major autoantibody response in theory is directed against Ro and La ribonucleoproteins. By taking into account the experience with orally administered antigens such as ovalalbumin and myelin basic protein), it seems probable that the Ro and La molecules or their immunodominant T-cell epitopes, when administered orally to Sjögren's syndrome patients, could induce immune tolerance to these autoantigens.[19]

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