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A Preliminary Evaluation of Azathioprine (Imuran®) in the Treatment of Multiple Sclerosis

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A theoretical approach to the unknown etiology of multiple sclerosis is presented in this preliminary study which reports the results of empiric treatment with azathioprine. Imuran® therapy produced stabilization of the disease, neurological improvement, and no progress of neurological dysfunction or loss of any regained function. Evidence points toward a viral-induced immunological defect. Abnormal gamma globulins found in the cerebral spinal fluid suggest an immunological etiology.

Multiple sclerosis is characterized by acute exacerbations of neurological dysfunction with intercurrent periods of improvement and quiescence. The lesions underlying this sequence of events are multi-focal plaques of demyelination, disseminated irregularly throughout the cerebral spinal axis, and occur in successive crops over a period of years. Demyelination begins at the peripheral myelin sheath, and spreads inwardly toward the axis cylinder, suggesting an external etiological cause. Some lymphocytic perivascular infiltration, with acute myelin edema, is found in fresh lesions.[1] A secondary gliosis develops in older foci.

There is evidence that abnormal gamma globulins are found in the cerebral spinal fluid of patients with multiple sclerosis.[2, 3] The clinical course, the pathological pattern of the acute foci, and the finding of abnormal gamma globulins relate as being similar to the rejection phenomenon of renal homotransplants.[4, 5] With this immunological implication of etiology, six patients with firm diagnoses of multiple sclerosis have been treated with Imuran®.

Methods and Procedures

Patients in this study have had a condition diagnosed as multiple sclerosis for a minimum of three years, with repetitive and progressive exacerbations documented for more than two years. In all patients, a trial of corticotrophin therapy failed to prevent progression of the disease process.

Pretreatment laboratory tests were required to be within normal limits, i.e., alkaline phosphatase < 4 Bodansky units, white blood count 4,000-

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10,000/cu mm, hemoglobin >11.0 gm/100 cc, and platelet count >150,000/cu mm. Serum protein electrophoresis also required normal values. Progress laboratory tests of WBC, hemoglobin, and platelet counts were made weekly for the first eight weeks; and monthly thereafter.

Cerebral spinal fluid (CSF), serum immunoglobulins, and viral antibody titers were determined pretreatment and at various times during treatment. These results will be discussed in a later paper, when statistical significance is established.

Patients were treated in the Oncology Division but were evaluated in the Neurology Department.

Results

No toxic effects were noted either clinically or by progress laboratory studies when Imuran was administered at a dosage of 50 mg twice a day.

Initial improvement was noted at four weeks, and maximum return of function was documented by the eighth week of therapy. In some cases, motor function improved in excess of the "Slight" neurological improvement noted in the chart below. However, this was felt to be only minimal neurological improvement. Due to the stability of the disease for a prolonged period, the patients were able to improve active functions of muscle groups through physiotherapy.

Discussion

"It is axiomatic that no immunological reaction takes place against the normal constituents of the body. No other situation is tolerable in health, and the multitude of serious diseases which develop when transgression of this rule takes place merely underlines its importance." [6]

Evidence points toward such a transgression of the self-recognition system in patients with multiple sclerosis. Theoretically, the immunological mechanism is complete at birth. Early evidence of an increased infectious disease viral titer in the CSF that is not abnormal in the serum[7] would seem to imply that a defect, infectious-disease-induced, alters the lymphocyte-recognition of the nervous system, which is now foreign to self. The delayed sensitivity then occurring results in production of antibodies and subsequently leads to rejection. This could account for the ab-

Patient	*Age*	*Sex*	*Imuran Dosage mg/kg/day*	*Months Treated*	*Neurological Improvement*	
B.T.	29	F	2.2	18	Visual+++	Vibratory++
V.S.	24	M	1.8	15	Visual+	Motor+
J.T.	38	M	1.8	13	Visual++	Motor+
M.B.	41	F	1.4	13	Visual+	Motor+
*E.B.	38	M	1.8	6	Visual+	Motor+
E.W.	42	M	1.6	6	Visual++	Motor+

Legend:
* Lost to follow-up after six months.
\+ Slight improvement.
++ Moderate improvement.
+++ Marked improvement.

normal globulin in the CSF and the pathological picture of early lesions with perivascular infiltration of lymphocytes and associated edema.

The retrospective history of multiple sclerosis, prior to diagnosis, varies and covers a span of several years. It is conceivable that exacerbation of neurological dysfunction exists for several years prior to recognition, thus accounting for the time delay between the viral infectious disease and documented onset of multiple sclerosis.

Prior to Imuran therapy, cyclic exacerbations and progressive neurological deterioration were documented. In agreement with Miller's findings, all patients were treated with corticosteroids and demonstrated continued progress of their disease.[8]

The six patients with a diagnosis of multiple sclerosis for at least three years, and a minimum of two years of prior cyclic acute exacerbations of neurological dysfunction, were successfully treated from 6 to 18 months with doses of 1.4-2.2 mg/kg/day of Imuran. The effects of Imuran therapy included stabilization of the disease, neurological improvement, no progression of neurological dysfunction or loss of any regained function. Clinically, it was not anticipated to regain neurological function but to achieve a stabilization of the disease. The neurological improvement is accounted for on the basis of reduction of edema. The most marked improvement has been in those patients with the most rapidly progressive disease and severe visual defects. No detectable improvement of ataxia has been recorded. The dosage schedule of Imuran used in this program is relatively safe and there is good patient tolerance.

In this preliminary report of treatment of multiple sclerosis with Imuran, an immunological etiology is suggested. The term autoimmune is not applicable. Abnormal gamma globulins and infectious disease viral titers found in the CSF suggest a viral-induced immunological defect.

Attempts are being made to determine the associated globulin component and the effect of Imuran on this immunoglobulin. This work will be reported at a later date.

Summary

This preliminary study presents a theoretical approach to the unknown etiology of multiple sclerosis, and reports the results of empiric treatment with azathioprine (Imuran®). Six patients have been treated. Abnormal gamma globulins found in the cerebral spinal fluid suggest an immunological etiology. The term autoimmune is not applicable; evidence points toward a viral-induced immunological defect. Imuran therapy produced stabilization of the disease and neurological improvement, with no progression of neurological dysfunction or loss of any regained function.

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