Multiple Sclerosis Treated with Antithymocyte Globulin — A Five Year Follow-Up

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SUMMARY: *Multiple sclerosis patients treated with antithymocyte globulin (ATG) were re-evaluated after five years. No long term benefit was found. Notably, the group of patients with an elevated gamma globulin to total protein ration in their C.S.F. and who did particularly well after treatment with ATG also failed to show any long term benefit. Few long term detrimental effects of ATG immunosuppression were identified. The implications of the results are discussed as they relate to the use of immunosuppression in multiple sclerosis.*

RÉSUMÉ: *Nous avons réévalué après 5 ans des patients souffrant de sclérose en plaques et qui furent traités à la globuline antithymocyte (ATG). Nous n'avons noté aucun bénéfice à long terme. Plus particulièrement, ces patients avec rapport gamma globuline/protéines totales élevé, qui furent ceux avec le meilleur résultat immédiat au ATG, n'ont montré aucun effet à long terme. Cependant nous n'avons pas observé non plus d'effets nocifs de l'immunosuppression à l'ATG. Enfin nous discutons des implications de l'imploi de l'immunosuppression dans la sclérose en plaques.*

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Following the demonstration of antithymocyte globulin's (ATG) effectiveness in suppressing established experimental allergic encephalomyelitis (Brendel et al., 1969; Land et al., 1969; Leiobowitz et al., 1968), it was used to treat the acute relapsing form (Brendel, 1971; Pirofski et al., 1971; Seland et al., 1974; Trouillas et al., 1970) and the chronic progressive form (Walker et al., 1976) of multiple sclerosis (M.S.). The encouraging results of preliminary studies have led to further investigation of immunosuppression in the treatment of M.S. Programs of intensive immunosuppression have been developed, in which several immunosuppressents, including ATG, are combined.

The reported benefit to M.S. patients treated with intensive immunosuppression (Brendel et al., 1975; Lance et al., 1975; Ring et al., 1974; Ring et al., 1976) and the lack of information on long term effects of ATG prompted a re-evaluation of M.S. patients treated with this medication.

METHOD

This study re-evaluated patients five years after they were treated with ATG. The results of the original prospective study, which included a one year follow-up, have been reported (Seland et al., 1974).

In the original study, twenty-one patients who had entered an acute stage of M.S. (Schumacher et al., 1965) were randomly assigned to either a control or a treated group (Table 1). The control group received adrenocorticotrophic hormone (ACTH) while the treated group received ACTH and ATG. One half of each group received a twenty-eight day course of therapy. This was decreased to fourteen days for the second half of each group in an effort to reduce complications arising from prolonged treatment.

In the present study, all surviving patients except for three out of province patients were evaluated by one of us. None of the examiners was aware of the type of therapy received by any patient. The evaluation documented the course of the illness since ATG treatment, and was followed by a standardized neurological examination. The results of the evaluations were used to score patients in each of eight functional systems. From the functional systems scores, a single disability status score (D.S.S.) was derived (Kurtzke, 1965). The score could range from zero to ten with zero representing an absence of clinically detectable disease and ten, death as a result of multiple sclerosis. A score of five would indicate a moderate disability, such as being unable to walk unaided more than several blocks.

Comparisons were made between the pre-treatment and five year post treatment disability status scores. T-tests were used for statistical evaluation of scores within the treatment groups, and analysis of covariance (Cochran and Cox, 1957) for evaluation between groups. In the latter analysis, the covariant was the pre-treatment score.

RESULTS

Patient population

Eighteen of twenty-one patients who had participated in the original study were alive five years after treatment. Of the three patients who died, two were in the control group and one was in the ATG treated group. One patient in the control

group received ATG following the completion of the original study and his score has been excluded from this evaluation.

Course of illness

At the time of re-evaluation, none of the surviving patients was in relapse. Although the majority of patients had experienced intermittent relapses in the intervening years, a few patients experienced a relatively benign course with few if any relapses. In others, the course of the illness had assumed the characteristics of chronic progressive multiple sclerosis (Schumacher et al., 1965).

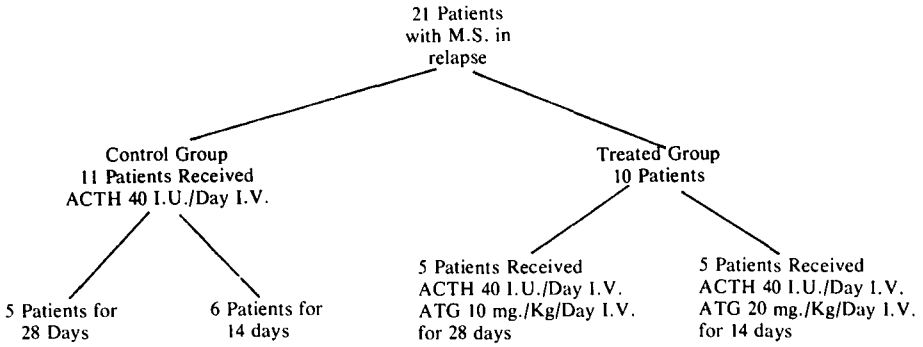
An accurate estimation of the relapse rate since ATG treatment was attempted but proved unsuccessful. Although a number of patients were able to provide details about relapses, in many cases this information was unavailable.

Treatment

Several patients had received intermittently various medications in the intervening years. These included prednisone, ACTH, azathioprine, megavitamins, and diet therapy. In the year prior to evaluation, only three patients had received medications for their disease. Two patients (patient 7, 18) were on prednisone (25 mgm. on alternate days, 10 mgm. every third day) and one patient (patient 16) was on azathioprine (50 mgm. every day). None of the patients received ACTH in the six months prior to evaluation.

TABLE I

Therapeutic Regimen Used By Seland et al



ACTH = Adrenocorticotrophic hormone

ATG = antithymocyte globulin

Complications

One patient (patient 15) developed osteomyelitis shortly after a course of ACTH and ATG and this may have been related to therapy. Five years later, he continues to require treatment for multifocal osteomyelitis.

Results of Re-evaluation

Pre-treatment and five year post treatment disability status scores for the control group are listed in Table 2. A statistical comparison of these results did not reveal a significant difference ($P > 0.5$).

The pre-treatment and five year post treatment disability status scores for the treated group are listed in Table 3. A comparison of these results failed to reveal any significant difference ($P > 0.5$). There was also

TABLE II

CONTROL GROUP

Clinical course of patients treated with ACTH alone as measured by D.S.S. scores

PATIENT	SEX	AGE AT RE-EVALUATION	LENGTH OF TREATMENT (days)	PRETREATMENT D.S.S.	POST TREATMENT D.S.S.	FIVE YEAR POST TREATMENT D.S.S.
1	M	-	28	9	5	10
2	F	57	28	6	5	3
3	M	52	28	4	1	3
4	M	-	28	4	8	10
5	F	30	14	6	6	6
5	F	45	14	7	5	6
7	M	47	14	6	6	7
8	M	39	14	6	6	6
9	M	49	14	6	6	7
10	M	31	14	6	1	2

ACTH = Adrenocorticotrophic hormone D.S.S. = Disability Status Score

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no significant difference between patients who were treated with ATG for twenty-eight days and patients treated for fourteen days ($P > 0.5$).

The results of the control and ATG treated groups were statistically compared. No significant difference was found.

The results of six patients in the ATG treated group who had elevated gamma globulin to total protein ratios (> 14%) in their pre-treatment C.S.F. were interesting. The pre-treatment and five year post treatment disability status scores are listed in Table 4. No significant difference was found between the pre-treatment and five year post treatment scores ($P > 0.5$). There was also no significant difference between this group and a comparable control group. (Table 5).

DISCUSSION

Various immunosuppressive agents have been used to treat patients with multiple sclerosis. Results have been disappointing. Patients usually showed minimal or transitory improvement. Resently, a number of papers have suggested that intensive immunosuppression may give long term benefit to patients with M.S. (Brendel et al., 1975; Lance et al., 1975; Ring et al., 1974, 1976). This regimen includes ATG, prednisone, and azathioprine. Thoracic duct canulation may be added to the program.

The present study re-evaluated M.S. patients five years after receiving ATG, in order to determine long term effects of this agent when used alone. The original study used ATG in comparable dosage to that used in intensive immunosuppression, and it was beneficial on a short term basis in acute relapsing M.S. (Seland et al., 1974). Furthermore, the trial found that patients with an elevated gamma globulin to total protein ratio (> 14%) in their C.S.F. were particularly benefited after treatment with ATG.

Of the twenty-one patients in the original study, eighteen were alive after five years. In the surviving patients, the course of the illness had been variable. In some patients, the course was benign, with few relapses and little disability. In others, it was characterized either by relapse and remissions with increasing disability after each relapse, or by a progressive deterioration.

A number of factors could have affected the results. Limited numbers of patients and a failure of randomization, to prevent an accumulation of young patients with a short duration of illness in the treated group, were difficulties encountered in the original study and were inherited by the present study. Although of limited importance in short term studies, the natural history of M.S. becomes an increasingly important variable in long term studies. Patients could not be matched for this variable at the time of the original study and the potential inequality of the two groups could significantly affect the results five years later. A number of patients received diet therapy, multivitamins, prednisone, ACTH, or azathioprine since the original study. While this treatment may be affecting the results, there is no definite evidence from blind controlled trials that any of these therapies alter the long term course of multiple sclerosis. The potential of these variables to alter the results is recognized, but to what extent they produce changes is not known.

The results of this study indicate antithymocyte globulin fails to provide long term beneficial effects to patients with multiple sclerosis. Since this series of patients received only one course of ATG, this is not unexpected. Since ATG has been shown to be of benefit on a short term basis, repeated courses of ATG may

TABLE III

TREATED GROUP

Clinical course of patients treated with ACTH and ATG as measured by D.S.S. scores

PATIENT	SEX	AGE AT RE-EVALUATION	LENGTH OF TREATMENT (days)	PRETREATMENT D.S.S.	POST TREATMENT D.S.S.	FIVE YEAR POST TREATMENT D.S.S.
11	F	28	28	6	1	6
12	F	31	28	7	6	6
13	F	-	28	6	2	10
14	F	29	28	6	1	1
15	M	42	28	6	6	6
16	F	36	14	7	6	6
17	M	37	14	7	6	7
18	F	34	14	6	2	9
19	M	32	14	6	5	6
20	F	25	14	9	3	9

ACTH = Adrenocorticotrophic Hormone D.S.S. = Disability Status Score A.T.G. = Antithymocyte Globulin

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be of benefit on a long term basis. The advantages to be gained would have to be weighed carefully against the disadvantages of side effects both immediate and long term. Although few long term side effects were identified in this study, the development of recurrent multifocal osteomyelitis in one patient following ATG treatment emphasizes the potential of this agent to cause morbidity. The recent development of ATG with fewer side effects may make the repeated use of this agent practical in the future, particularly in patients in acute relapse who are unresponsive to other forms of therapy and who have an elevated C.S.F. gamma globulin to total protein ratio.

The reports of long term benefit from intensive immunosuppression are of interest in view of this study. Since ATG does not produce long term benefit when used alone, the benefit derived from this approach would appear to depend more on continuing immunosuppression. If the results of these uncontrolled trials are confirmed by blind controlled trials, the use of prolonged immunosuppression may be of value in the treatment of some patients with M.S. Considerable care would have to be taken in the selection of patients, however, as the complications of prolonged immunosuppression could easily out-weigh the advantages.

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TABLE IV

TREATED GROUP

Clinical course of patients with an elevated C.S.F. gamma globulin to total protein ratio and who were treated with ACTH and ATG.

PATIENT	PRETREATMENT D.S.S.	POST TREATMENT D.S.S.	FIVE YEAR POST TREATMENT D.S.S.
11	6	1	6
12	7	6	6
13	6	2	10
14	6	1	1
19	6	5	6
20	9	3	9

C.S.F.=Cerebrospinal fluid
ACTH=Adrenocorticotrophic hormone
ATG=Antithymocyte globulin
D.S.S.=Disability Status Score

TABLE V

CONTROL GROUP

Clinical course of patients with an elevated C.S.F. gamma globulin to total protein ration and who were treated with ACTH only.

PATIENT	PRETREATMENT D.S.S.	POST TREATMENT D.S.S.	FIVE YEAR POST TREATMENT D.S.S.
2	6	5	3
3	4	1	3
4	9	8	10
5	6	6	6
9	6	6	7

C.S.F.=Cerebrospinal fluid
ACTH=Adrenocorticotrophic hormone
D.S.S.=Disability Status Score

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