

SUPPRESSOR FACTOR IN PLASMA OF AMINOPHYLLINE TREATED RENAL TRANSPLANTED PATIENTS

Z Shapira, B Shohat, A Yusim, C Servadio

Petah Tiqva and Tel Aviv University Sackler School of Medicine, Israel

Summary

Eleven of 15 patients with a first acute rejection episode following cadaveric renal transplantation resumed adequate graft function and increased peripheral blood suppressor T-lymphocyte activity following treatment with 'pulse' methylprednisolone and aminophylline (1000mg orally daily for 14 days). Four of 11 patients treated with 'pulse' methylprednisolone alone resumed adequate graft function, but only two of these had elevated peripheral blood suppressor T-lymphocyte function. Nine of the 11 responding patients exhibited plasma suppressor activity to xenogenic graft versus host reaction but such activity was not observed in the plasma of any of the 11 patients who received methylprednisolone alone.

Introduction

Recently we described observations on the lack of suppressor T-lymphocytes (STL) in the peripheral blood of renal transplant patients during steroid resistant acute rejection episodes (ARE). About 75 per cent of those patients respond to administration of aminophylline with reappearance of active STL in the peripheral blood and resumption of adequate renal graft function.

We suggested that the aminophylline released and activated STL from lymphopoietic organs into the peripheral blood thus re-setting the immunological balance in favour of suppression [1].

The present study was undertaken to determine whether a soluble plasma factor could be recognised in patients with such a response to aminophylline.

Materials and methods

Fifty-eight uraemic patients received a first cadaver kidney graft in our centre during the period from February 1981 to February 1982. All of them were treated with 0.3mg/kg/day prednisolone and 1.5mg/kg/day azathioprine from the first day after transplantation.

Antirejection therapy included three to six 'booster' doses (1000mg each daily) of methylprednisolone (IVMP). Twenty-six patients with their first ARE who were found resistant to this antirejection therapy were studied. They were divided into two groups: one group included the first 15 patients of the study (the treated group), and the other eleven recipients served as a control group.

Both groups, as well as all our patients with ARE, were monitored every second day after diagnosis of rejection for STL in their peripheral blood and their suppressor ability and for possible suppressor activity of their plasma. Patients of the treated group received aminophylline 1g daily orally for 14 days after cessation of the IVMP therapy. There were no significant differences in either group in regard to age and sex of the recipients, primary kidney disease, duration of haemodialysis, pretransplant blood transfusions and HLA-A-B-DR mismatches. No patient had more than two identities in HLA-A-B and more than one in HLA-DR.

Diagnosis of ARE was established by local graft tenderness, sudden decrease in urine output and significant increase in serum creatinine. At the same time, other complications that could simulate ARE were excluded.

The presence of STL was demonstrated by the method of Shore et al [2], who found that theophylline inhibits the ability of a distinct T-cell subset (STL) to form E-rosettes.

The suppressor ability of the STL or of the plasma was assessed by the local xenogenic graft versus host reaction (GVHR) method as described by Shohat et al [3,4]. STL (5×10^4) or plasma (0.2ml) were mixed with non-treated lymphocytes (5×10^6) from healthy donors and inoculated into the ear of immunosuppressed rats. Absence of a positive reaction was considered to be due to the presence of active STL or soluble suppressor factor in the plasma.

Results

In both groups none or only a small amount of STL, and no suppressor activity of the plasma could be found during the period of therapy with IVMP.

Eleven of the 15 recipients treated with aminophylline responded with resumption of adequate graft function and reappearance of increasing amounts of STL in their peripheral blood. In nine of these patients suppressor activity of the plasma was also noted.

In the control group of 11 patients, four resumed adequate graft function and in two of them the amount of STL increased. However, no STL activity or suppressive ability of the plasma could be detected. (Table I).

Discussion

Similar to previous observations [1] this study again suggests that theophylline is capable of releasing active STL to the peripheral blood and therefore might be effective in reversing ARE. An inhibitory effect of the theophylline on the immune

TABLE I. Number of patients with STL, positive xenogenic GVHR - with STL, and with plasma in each group

		Days After Diagnosis of ARE						
		2	4	6	8	10	12	14
No. of patients with significant presence of STL in the peripheral blood (more than 10%)	Treated Group	0/15	0/15	0/15	2/15	9/15	11/15	11/15
	Control Group	0/11	0/11	0/11	1/11	2/11	2/11	2/11
No. of patients with detected STL activity by the xenogenic GVHR	Treated Group	0/15	0/15	0/15	0/15	8/15	11/15	11/15
	Control Group	0/11	0/11	0/11	0/11	0/11	0/11	0/11
No. of patients with detected plasma suppressor activity by the xenogenic GVHR	Treated Group	0/15	0/15	0/15	0/15	6/15	8/15	9/15
	Control Group	0/11	0/11	0/11	0/11	0/11	0/11	0/11

response has been described by Watson et al [5] and by Ljungstrom et al [6] although other modes of function were suggested.

The observation that the plasma of aminophylline treated patients (nine out of 15) showed immune suppressive activity by inhibiting the xenogenic GVHR suggests that there might be a soluble suppressor factor in the plasma which has been produced and secreted by the aminophylline activated STL. This assumption is supported by the fact that such a factor could not be recognised in the patients from the control group who resumed their kidney graft function without the aid of aminophylline. Laboratory experiments show that soluble factors produced and released from different subsets of T-cells participate in the regulation of immune processes [7, 8].

The importance of an isolated purified and concentrated suppressor factor for clinical use seems to be obvious. Further experiments should show if aminophylline could be used to reach this goal.

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References

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Address for correspondence: Z Shapira, Transplant Unit, Beilinson Medical Centre, Petah Tiqva and Tel Aviv University Sackler School of Medicine, Israel