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OKT3 MONOCLONAL ANTIBODY REVERSAL OF ACUTE RENAL ALLOGRAFT REJECTION UNRESPONSIVE TO CONVENTIONAL IMMUNOSUPPRESSIVE TREATMENTS

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ORTHOCLONE OKT3 was shown, in a randomized multicenter trial for acute rejection of cadaveric renal transplants, to reverse 94 percent of the rejections as contrasted with a 75 percent reversal rate obtained with conventional steroid treatment (P=0.009). This superior reversal rate with OKT3 was reflected in an improved one-year graft survival rate (62 percent) as compared with the steroid-treated group (45 percent). We now present the results of a clinical trial involving 173 patients with acute renal allograft rejection that failed to respond to conventional immunosuppressive therapies. OKT3 monoclonal antibody was given for a 10-14 day course and the dosage of other immunosuppressive drugs was reduced. Acute rejection was reversed by OKT3 monoclonal antibody in 121 patients (70 percent) and actuarial graft survival at 6 months was 52 percent. The therapeutic properties of OKT3 are ascribed to blocking of the T3-antigen-receptor

complex of T lymphocytes and consequent blocking of cytotoxic T lymphocyte rejection of the allograft.

INTRODUCTION

Transplantation of renal allografts is the preferred treatment for many patients with terminal renal failure. Immunological rejection is abated by HLA matching of donor and patient and by immunosuppressive agents, notably corticosteroids, azathioprine, polyclonal anti-thymocyte globulin and lately cyclosporine, but rejection episodes still occur in a majority of patients. Rejection episodes are conventionally treated with high-dose steroid pulses (Glass et. al., 1983) or with anti-thymocyte globulin (Shield et. al., 1979).

T cells, which are involved in cellular rejection of allografts, recognize the "foreign" nature of the graft by antigen recognition structures in the cell surface (Mak and Yanagi, 1984). The antigen recognition structure is a disulfide-linked heterodimer which consists of two glycosylated polypeptide chains. OKT3 recognizes one of three associated polypeptide chains that comprise the T3 complex (Kung et. al., 1979; van den Elsen et. al., 1984). The T3 complex transmits an intracellular signal after the T cell has recognized antigen (Imboden et. al., 1985; Reinherz et. al., 1982). Binding of OKT3 to the T3 component on the T cell surface blocks T cell function *in vitro* (Chang et. al., 1981) and also *in vivo*, as the efficacy of OKT3 in reversing the acute rejection of renal transplants testifies (Goldstein et. al., 1985).

We have previously reported that the monoclonal antibody OKT3 is effective in the treatment of acute rejection of renal allografts (Goldstein et. al., 1985). In this study, 123 patients undergoing acute rejection of cadaveric renal transplants were treated with either OKT3 5 mg i.v. daily for a mean period of 14 days, with concomitant lowering of azathioprine and prednisone (63 patients), or with conventional high-dose steroid therapy (60 patients). Similar immunosuppressive maintenance therapies of azathioprine and prednisone were subsequently administered to both groups and recurrent episodes of rejection were similarly treated with high-dose steroids or anti-thymocyte globulin. The results of the study

showed a superior efficacy of reversal of rejection by OKT3 (94 percent) which was significantly higher (P=0.009) than that achieved with conventional steroid treatment (75 percent).

A second rejection was common to both groups, 66 percent of patients initially treated with OKT3 and 73 percent in patients treated with conventional steroids. Subsequent kidney loss due to repeated rejection was also similar in both groups, 33 percent and 38 percent for OKT3 therapy and conventional steroid therapy, respectively. However, based on the superior reversal rate obtained with OKT3 therapy, at one year the OKT3 treated group demonstrated an improved graft survival rate (62 percent) as contrasted to the steroid treated group (45 percent).

We report here on the successful use of OKT3 in patients with acute renal allograft rejection that failed to respond to conventional therapy.

METHODS

Production of OKT3

The OKT3-producing hybridoma, characterization of the OKT3 IgG_{2a} antibody and its preparation as a sterile pyrogen-free formulation for parenteral dosage by weight of immunoglobulin, have been reported (Goldstein et. al., 1985; Kung et. al., 1979).

Eligibility Criteria

The diagnosis of acute renal allograft rejection and reversal of rejection were based on the usual criteria of failing renal function and inflammation of the graft (Shield et. al., 1979). In each case it was required that by these criteria the rejection episode was not responding to conventionally adequate courses of high-dose steroid pulses and anti-thymocyte globulin, or that either of these agents was contraindicated or unavailable; reasons for contraindication included chronic infections or severe diabetes mellitus for steroids and hypersensitivity or adverse reactions for anti-thymocyte globulin. Each patient was informed of the investigational status of OKT3

and signed a consent form. Use of OKT3 in each participating center was approved by an Institutional Review Board.

OKT3 Treatment Regimen

5 mg OKT3 was given daily by intravenous push for 10-14 days. Other immunosuppressive drugs were reduced in dosage during this period, with resumption to maintenance levels thereafter. During early studies with OKT3 five renal rejection patients (including two in the present study) developed severe pulmonary edema following the first injection of OKT3; all five patients had pre-existing fluid overload. After this association was recognized, as a precaution against fluid overload, OKT3 therapy was initiated only when chest X-rays were deemed satisfactory and when no more than 3 percent gain in body weight was observed during the preceding week, in addition to a satisfactory overall clinical assessment. A bolus injection of 500 mg methylprednisolone or 1 gm hydrocortisone was given 1-6 h before the first injection of OKT3 to alleviate chills and fever that may accompany the first dose.

Evaluation

The status of the kidney graft and the condition of the patient were formally evaluated at the conclusion of OKT3 therapy and six months later. Actuarial survivals were determined by life table analysis (Gross and Clark, 1975).

RESULTS

The 173 patients reported comprised 115 males and 58 females, ranging in age from 2 to 65 (median 33) years, of whom 31 patients had diabetes mellitus. 140 patients were rejecting a first renal allograft, 28 a second, 4 a third and 1 a fourth renal allograft. 130 patients were rejecting grafts from cadavers and 43 were rejecting grafts from living donors, 42 related and one unrelated.

The patients received treatment at 33 centers, 29 in the U.S.A., 2 in France, 1 in Italy, and 1 in South Africa. The immunosuppressive regimens in use at the time that graft rejection was recognized clinically included azathioprine plus prednisone (69 patients), azathioprine, prednisone and anti-thymocyte globulin, (16 patients), cyclosporine and prednisone (50 patients) and cyclosporine, azathioprine, and prednisone (30 patients). Eight patients had a combination of immunosuppressive treatments combining the above regimens. After diagnosis of acute renal allograft rejection 66 patients were unsuccessfully treated with high dose steroid pulses and anti-thymocyte globulin for 24 ± 3 days (mean ± SEM) before OKT3 was initiated, 100 patients were unsuccessfully treated with high dose steroid pulses alone for 10 ± 1 days and 7 patients were unsuccessfully treated with anti-thymocyte globulin for 17 ± 7 days before initiation with OKT3 treatment (Table 1).

TABLE 1. OKT3 Monoclonal Antibody Reversal of Acute Renal Allograft Rejection in Patients that Could not be Reversed by Conventional Treatments

Failed treatment for current rejection	Days from first rejection treatement to first OKT3 mean ± SEM	Reversal incidence (percent)	
Increased steroids and anti-thymocyte globulin	24 ± 3	49/66	(74)
Increased steroids	10 ± 1	67/100	(67)
Anti-thymocyte globulin	17 ± 7	5/7	(71)
	15 ± 1	121/173	(70)

Adverse Reactions and Patient Survival

Flu-like symptoms occurred, mainly after the first dose of OKT3. On the first day these comprised pyrexia and chills (38 percent of cases), headache (20 percent), vomiting or diarrhea (10-12 percent). On the second day, the incidence of these symptoms was reduced: pyrexia and

chills (15-28 percent), headache (14 percent) and nausea, diarrhea or vomiting (10-13 percent). During the remaining days of OKT3 treatment only pyrexia (18 percent) persisted in an incidence greater than 10 percent.

Two patients developed severe pulmonary edema after the first injection of OKT3 and these patients, with pre-existing fluid overload, were among the first 33 patients treated, during which period no special precautions were taken with respect to fluid overload. No cases of severe pulmonary edema occurred among the remaining 140 patients screened as above for fluid overload prior to the first injection of OKT3.

168 of the patients (97 percent) survived to the time of analysis with 84 patients observed for at least 6 months. No deaths were directly related to OKT3 therapy. Actuarial patient survival at 6 months was 95 percent.

Reversal of Rejection

Reversal rates are given in Table 1. Rejection was reversed by OKT3 in 70 percent of patients and results were similar regardless of which conventional treatment regimens had been unsuccessfully used prior to OKT3 therapy.

Kidney Graft Survival

Figure 1 is based on kidney graft survival from time of first treatment with OKT3, according to life table analysis, and signifies an actuarial 6-month graft survival of 52 percent, all deaths being considered as losses of kidney function regardless of the status of the graft at the time of death.

DISCUSSION

Treatment with OKT3, coupled with reduction of preceding immunosuppressive medication, has been shown in a previous randomized study to be superior to high dose steroid pulses in reversing acute renal allograft rejection (Goldstein et. al., 1985). The use of OKT3 as

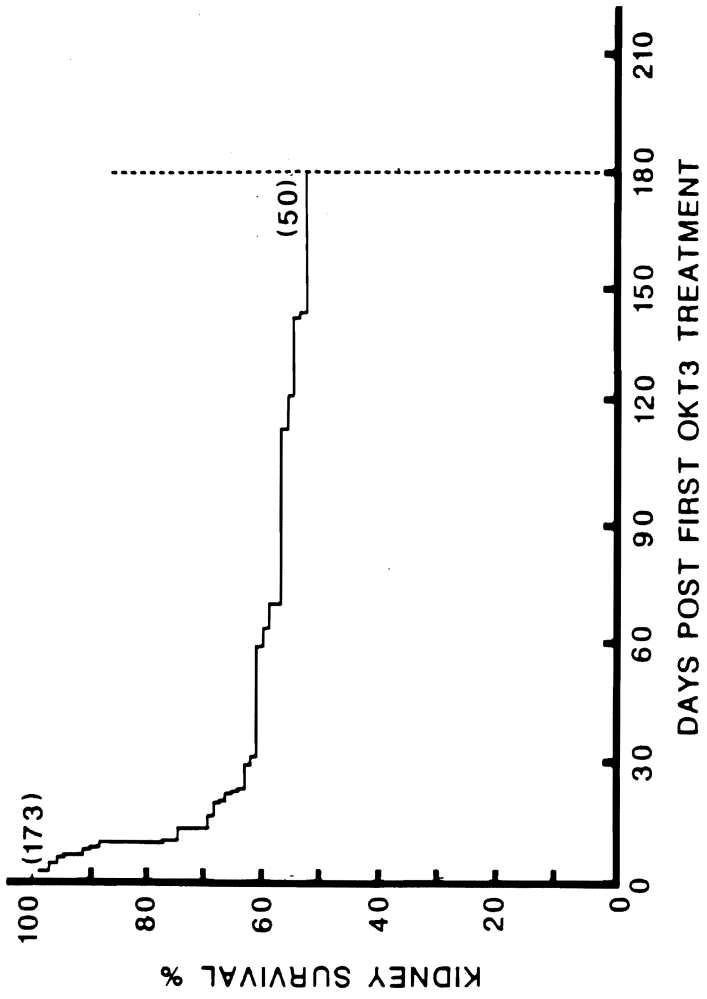

Figure 1. Life table analysis of kidney graft survival in patients treated with OKT3 for acute renal allograft rejection unresponsive to conventional immunosuppressive treatments. Numbers of patients with functioning kidney grafts being followed at indicated time points are indicated in parenthesis.

the sole immunosuppressive agent has also been explored in a preliminary open study for the prevention of acute renal allograft rejection, with administration from the time of transplantation (Kreis et. al., 1985). An initial protocol was discontinued after a brief period of time because all patients in the OKT3-treated group experienced acute rejection episodes at the end of the OKT3 treatment period, necessitating the introduction of steroids about 12 days posttransplant. Evaluation of this preliminary study led to the conclusion that OKT3, albeit a major immunosuppressive agent, did not induce tolerance over this short time period; prolonged administration was limited by the development of host antibodies to OKT3. A second protocol was initiated to assess whether the immunogenicity to OKT3 could be reduced by concomitant administration of low dose steroids and azathioprine. Host antibody formation was reduced and most patients could be treated for thirty days. The results of this randomized study are not yet conclusive but do offer promise that the prophylactic use of OKT3 may be worthwhile in renal allograft transplantation to reduce renal rejection and improve graft survival.

The present study was directed to evaluating the potential of OKT3 in reversing acute renal allograft rejection that had not responded to conventional treatment with high dose steroids and anti-thymocyte/lymphocyte globulin. The study attests to the efficacy of the OKT3 regimen described here in combating acute rejection and in maintaining renal function when other therapies have failed, and it also supplies a clinical alternative when other therapies may be contraindicated for reasons such as sensitivity to anti-thymocyte globulin, intercurrent infection or severe diabetes mellitus. Reversal of the acute rejection episode in 70 percent of patients, after the failure of conventional therapy, led to an actuarial kidney graft survival of 52 percent at 6 months. The several reports of 12-month graft survival rates of more than 80 percent refer to rates for all included patients receiving kidney transplants, many of whom either do not experience acute rejection or respond readily to conventional therapy, and do not bear comparison with the data reported here for patients experiencing acute rejection that is resistant to conventional therapy (Kahan et. al., 1985; Najarian et. al., 1985; Canadian Transplant Group, 1983).

The flu-like symptoms accompanying OKT3 therapy were particularly marked on the first day and were much reduced thereafter, which is consistent with the view that they are a consequence of acute elimination of the T lymphocyte population which is opsonized by OKT3 antibody. Respiratory symptoms progressed to severe pulmonary edema in two patients with pre-existing fluid overload. Once this uncommon complication of a first dose of OKT3 was traced to pre-existing fluid overload that circumstance was avoided in the remaining patients by monitoring for gain in weight and by radiography of the chest beforehand.

OKT3 is a monoclonal antibody and therefore virtually free of the variations in constitution, concentration and potency that hamper therapy with polyclonal antibodies derived from antisera. Three mechanisms, probably additive, deserve consideration with respect to the therapeutic effects of OKT3; namely, blocking of T3 function (Chang et. al., 1981), modulation of T3 (Chatenoud et. al., 1982) (phenotypic reduction of T3 and antigen-receptor expression on the T lymphocyte surface caused by antibody) and cytoelimination of T lymphocytes (Miller et al., 1981; Colvin et. al., 1981). Cytoelimination is not likely to be the only mechanism because although monoclonal antibodies to other components of the human T lymphocyte surface will opsonize T lymphocytes and cause their rapid elimination by the reticuloendothelial system, as does OKT3, they do not substantially avert renal allograft rejection (Carpenter et. al., 1983; Takahashi et. al., 1983; Thurlow et. al., 1983).

OKT3 monoclonal antibody provides a new and highly selective method of blocking T lymphocyte function and averting immunological rejection of a renal allograft; further studies will be needed to define its optimal use in transplantation.

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