

## **RESCUE OF STEROID-RESISTANT REJECTIONS WITH OKT3.PAN**

E Rivolta, A De Vecchi, A Tarantino, F M Egidi, A Vegato,  
C Ponticelli

*Ospedale Maggiore, Milan, Italy*

### **Summary**

Monoclonal antibody OKT3.PAN was given (5mg intravenously daily for 9–22 days) as the only immunosuppressive agent to nine renal transplant patients with severe steroid-resistant acute rejection. Seven patients regained good renal function; five of them experienced a second rejection episode, which was reversed with two to four methylprednisolone pulses. The seven patients have now good renal function 3–23 months after transplantation. There were no severe complications due to the monoclonal antibody.

### **Introduction**

OKT3.PAN (OKT3) is a murine monoclonal antibody directed against human T cells which was developed by Kung et al [1]. It was obtained from a hybridoma produced by the procedure of Kohler and Milstein [2], from which OKT3 was purified biochemically. A sterile solution suitable for intravenous administration, prepared by the Ortho Pharmaceutical Corporation Laboratories (Raritan, NJ, USA), has been made available for pilot studies in man. Some reports about the therapeutic use of this monoclonal antibody have already been published [3–5]. We report here our experience with OKT3 used for treatment of severe, steroid-resistant acute rejection in renal transplant patients.

### **Methods and patients**

In our Unit the diagnosis of rejection is based on a serum creatinine increase of at least 25 per cent, not attributable to causes other than rejection. Decreased urine volume, decreased urine sodium excretion, increase in proteinuria, body weight gain, kidney swelling and tenderness, hypertension and fever are considered to support the diagnosis [6]. Fine needle aspiration biopsy [7] and renal biopsy are also done to confirm the diagnosis or assess the prognosis [6].

Severe steroid-resistant rejections are defined as early acute rejections which after two or more intravenous high-dose methylprednisone pulses still show progressive increase in plasma creatinine to above 10mg/dl. Nine patients (5 men, 4 women, aged 24–44 years) with first rejection episodes fulfilling these criteria were included in this study. Eight had received their kidneys from cadavers and one from a living related donor. Two patients (BA, CP) were on conventional therapy [8] and seven on Cyclosporin A (initial dose 15mg/kg) plus low dose methylprednisone (initial dose 16mg/day). During the course of treatment with OKT3, the azathioprine or Cyclosporin A was stopped but oral maintenance steroid therapy continued. Fluid overload was corrected, when present, by dialysis or diuretics before the first OKT3 administration. Moreover, the first OKT3 dose was preceded by 0.5g of intravenous methylprednisone. OKT3 was given for 9–22 days at a daily dose of 5mg, administered as intravenous boluses.

## Results

Two patients did not improve with OKT3 therapy. One had a vascular rejection, in the other the OKT3 was started too late in the rejection, after high dose methylprednisone therapy and antilymphocyte globulin administration had failed. Both were high risk patients, one due to hyperimmunization and one to immunological failure of a previous transplant. The other seven patients showed improvement of renal function on OKT3 (Table I). Four of them had further rejections 4–20 (mean 9) days after OKT3 treatment was stopped. In another patient a second rejection episode occurred during the OKT3 course (12 days after the beginning). OKT3 was stopped and rejection was controlled and reversed by 2x0.5g methylprednisone, as intravenous pulses.

The first injection of OKT3 caused chills and temperatures between 37.5° and 40° in eight patients. No wheeze or dyspnoea was observed. As late complications, two patients had lip herpes simplex lesions, one had herpes keratitis (70 days after OKT3). One patient on Cyclosporin A developed a nocardia asteroides pneumonia nine months after the OKT3. All these complications completely healed after appropriate therapy.

## Discussion

Some recent reports have confirmed the role of the monoclonal antibody OKT3 for treatment of rejection episodes. Thistlethwaite et al [4] administered OKT3 as first therapy to 30 renal transplant recipients with acute rejection. OKT3 caused selective loss of T cells from the circulation within minutes and reversed rejection in all the patients within 2–8 days. Although 20 patients had further rejection episodes, 20 of the 30 patients had excellent graft function 6–44 months after the OKT3. Norman [5] gave OKT3 to 31 patients as the first anti-rejection treatment. Rejection was reversed in all cases. The same investigator used OKT3 to rescue 15 conventional drug-resistant rejection episodes. In 13 of them, rejection was reversed. The one year graft survival for Norman's 46 patients was 70 per cent.

TABLE I. Characteristics of the patients and renal function before and after OKT3 therapy

| Patient | Age (years) | Sex | Day of onset of rejection | MP pulses | No. OKT3 doses | before rejection | PLASMA CREATININE (mg/dl) | at present | Follow-up (months) |
|---------|-------------|-----|---------------------------|-----------|----------------|------------------|---------------------------|------------|--------------------|
|         |             |     |                           |           |                |                  | peak                      | after OKT3 |                    |
| BA      | 26          | F   | 4                         | 5         | 21             | 2.6              | DIALYSIS                  | 9.4        | 3.4                |
| CP*     | 43          | F   | 6                         | 2         | 22             | 0.9              | DIALYSIS                  | 4.0        | 2.0                |
| BL*     | 44          | M   | 13                        | 3         | 16             | 1.9              | DIALYSIS                  | 4.0        | 2.0                |
| TG**    | 29          | M   | 37                        | 5         | 12             | 1.7              | 9.8                       | 7.7        | 2.8                |
| CL*     | 40          | M   | 31                        | 5         | 15             | 1.5              | DIALYSIS                  | 1.5        | 2.4                |
| VC      | 36          | F   | 5                         | 3         | 10             | 3.1              | DIALYSIS                  | TRANSPLANT | NEPHRECTOMY        |
| GC      | 24          | M   | 6                         | 2         | 10             | 1.7              | 13.6                      | 2.0        | 1.9                |
| QL*     | 41          | F   | 4                         | 4         | 10             | 1.9              | 10.0                      | 3.3        | 2.7                |
| MR      | 43          | M   | 5                         | 5         | 9              | DIALYSIS         | DIALYSIS                  | TRANSPLANT | NEPHRECTOMY        |

\* Patients with a second rejection episode *after* OKT3

\*\* Patient with a second rejection episode *during* OKT3

Our experience confirms that OKT3 is effective for the treatment of severe steroid-resistant rejection, since this complication was reversed in seven of nine patients (77%). Five patients had second rejection episodes, one during treatment and the other four a few days after OKT3 had been stopped. However, in all the patients these rejections responded to methylprednisone pulse therapy.

The most worrying side effect of OKT3 is the fever and chills which almost always occur 20–40 minutes after the first OKT3 injection. To avoid severe side effects (shaking chills, with fever to 101°C, shortness of breath and diffuse wheeze over the lung fields) described by another group [3] we gave 0.5g methylprednisone intravenously a few hours before the first OKT3 injection to all the patients. This procedure abated the fever due to rejection and probably decreased the mass of lymphocytes destroyed by OKT3. In this way, after the first OKT3 administration, fever and chills were generally less severe. The infrequent occurrence of acute pulmonary oedema following the first OKT3 injection, described by others [9], was prevented by guarding against fluid overload and ensuring that the weight gain was less than three per cent of the weight in the week preceding the start of OKT3. Three patients developed herpes virus infections, suggesting that OKT3 may expose the patients to infectious complications. However, none of the infections were severe and they healed completely in all cases.

On the basis of this experience, we feel that OKT3 is a powerful weapon in cases of severe steroid-resistant renal allograft rejection and, provided some precautions are taken, it is relatively safe.

## References

- 1 Kung PC, Goldstein G, Reinherz EL et al. *Science* 1979; 206: 347
- 2 Kohler G, Milstein C. *Nature* 1975; 256: 495
- 3 Cosimi AB, Burton RC, Colvin RB et al. *Transplantation* 1981; 32: 535
- 4 Thistlethwaite JR Jr, Cosimi AB, Delmonico FL et al. *Transplantation* 1984; 38: 695
- 5 Norman DJ, Barry JM, Henell K et al. *Transplant Proc* 1985; 15: 39
- 6 Banfi G, Imbasciati E, Tarantino A et al. *Nephron* 1981; 28: 222
- 7 Egidi F, De Vecchi A, Banfi G et al. *Transplant Proc* 1985; 17: 61
- 8 Ponticelli C, De Vecchi A, Tarantino A et al. *Kidney Int* 1983; 3 (suppl 14): 85
- 9 Goldstein G, Schindler J, Sheahan M et al. *Transplant Proc* 1985; 17: 129