Letter to the editor

TRANSPLANT International

Transplant Int (1988) 1: 116–117

First clinical experience with a new TCR/CD3-monoclonal antibody (BMA 031) in kidney transplant patients

W. Land[1], G. Hillebrand[3], W.-D. Illner[1], D. Abendroth[1], E. Hancke[1], S. Schleibner[1], C. Hammer[2], and J. Racenberg[4]

[1] Abteilung für Transplantationschirurgie, Chirurgische Klinik und Poliklinik, [2] Institut für Chirurgische Forschung, and [3] Nephrologische Abteilung, Medizinische Klinik I, Klinikum Grosshadern der Universität, Marchioninistrasse 15, D-8000 München 70, Federal Republic of Germany
[4] Behring-Werke AG, D-3550 Marburg 1, Federal Republic of Germany

The antibody used is a murine monoclonal antibody (IgG2b-type) with specificity against the alpha- and beta-chain of the TCR/CD3 receptor molecule; it has been developed and produced by the Behring Company (Marburg, FRG) [1, 2]. Characteristically, BMA 031 activates human T-lymphocytes in vitro to a lesser degree than monoclonal antibodies with CD3 specificity of different subclasses [3, 4].

We have used BMA 031 prophylactically in conjunction with triple drug induction treatment in kidney-transplanted patients with an increased immunological risk (preformed lymphocytotoxic antibodies > 30% against test panel or retransplantation following previous graft loss due to immunological causes). Two different immunosuppressive protocols have been applied (protocols 1 and 2) in terms of a phase-II trial.

Protocol 1

Nine patients received BMA 031 intravenously at a daily dose of 5 mg over a period of 7 days postoperatively in conjunction with ciclosporin (6 mg/kg orally), azathioprine (2 mg/kg) and methylprednisolone (500 mg→30 mg daily). During or after administration, no major clinical side effects (in particular: high fever, chills, lung edema) were observed whatsoever in contrast to other commercially available agents. The actual 1 year patient survival rate is 100% and the graft survival rate 89%. However, seven of nine patients (78%) developed histologically proven acute rejection episodes, requiring further antirejection treatment (steroids, ALG, ATG). In four patients (44%), rejection occurred either during or immediately after treatment with BMA 031.

During application of BMA 031, the total lymphocyte number was reduced by 63% within the first 3 days. Lymphocyte subsets labelled with monoclonal antibodies CD3 decreased by 56%, CD4 by 65%, and CD8 by 73%. Normal values were again reached between days 7 and 10 after beginning therapy. With regard to the remarkable absence of clinical side effects but the relatively high incidence of reversible rejection episodes, we changed our immunosuppressive protocol (in terms of approaching immunomodulation) as follows.

Protocol 2

Ten consecutive patients recently received BMA 031 in terms of a "double-shot" application: 1st injection of 50 mg intravenously during surgery; 2nd injection of 50 mg intravenously 48 h post-transplantation. In these patients triple drug induction treatment was given as mentioned in protocol 1.

Over an observation period from 4.5 months to 2 weeks we observed no rejection episodes in these patients. Graft function is perfect in all cases at the present time (4.5 m; 4 m; 3.5 m; 3 m; 2.5 m; 2 m; 1 m; 1 m; 3 w; 2 w). BMA 031 had a strong impact on total lymphocyte counts. After the first injection, their number was reduced to less than 10% of circulating mononuclear cells. Another reduction was

Offprint requests to: W. Land

observed after the second injection. Lymphocytes started to recover 5 days after application. Lymphocyte subsets followed this behavior, with all T-cell populations largely disappearing from the peripheral blood. Seven days after the start of therapy, all T-cell subsets approach pretransplant values.

Despite the tenfold dosage of BMA 031, again no side effects have been observed during or after administration. According to our preliminary and still limited clinical experience, the new monoclonal antibody BMA 031 appears to be an agent that can be administered extremely safely.

The efficacy of this new monoclonal antibody cannot be assessed so far on the basis of a statistical analysis because of the small number of patients in the trial. However, the excellent 1-year graft survival rate in the first group of patients, as well as the complete absence of rejection episodes in the second group of patients, might suggest that a new kind of immunomodulation rather than immunosuppression could be achieved, as has recently been discussed by others [2]. Thus, these preliminary data are of interest against the background of discussion of T-cell deletion/depletion and/or suppressor-cell-induced unresponsiveness. Further immunological studies devoted to this question are in progress.

References

1. Jetsukawa W, Faure F, Lipinski M, Triebel F, Hercend T (1987) A novel subset of human lymphocytes with a T-cell receptor gamma complex. J Exp Med 166: 1192-1197
2. Kurrle R, Lang W, Kanzy EJ, Seiler FR (1986) Distinction of two CD3-monoclonal antibodies in respect to the effectivity to modulate the induction of IgM and interferon synthesis. Behring Inst Mitt 80: 48-58
3. Kurrle R, Seyfert W, Trautwein A, Seiler FR (1986) T-cell activation by CD-3 antibodies. In: Reinherz EL, Haynes BF, Nadler LM, Bernstein ID (eds) Leukocyte typing II, vol 1: Human T-lymphocytes. Springer, Berlin Heidelberg New York, pp 137-145
4. Nashan B, Wonigeit K, Schwinzer R, Schlitt HJ, Kurrle R, Pichlmayr R (1987) A fine specificity of a panel of antibodies against the TCR/CD3 complex. Transplant Proc 19: 4270-4272