PROGNOSTIC SIGNIFICANCE OF B AND T CELL ANTIBODIES IN KIDNEY TRANSPLANTATION

V Lenhard, W Rettwitz, K Dreikorn, L Röhl

University of Heidelberg, FRG

Summary

The prognostic significance of pre- and post-transplant B and T cell antibodies was studied in 183 cadaver kidney transplantations. Our results confirm previous reports that a successful kidney transplantation can be carried out in spite of a positive crossmatch due to B cell antibodies. However, it is doubtful whether such antibodies have a protective effect. The success rate seemed to be higher only in patients with preformed cold antibodies. The occurrence and persistence of allogeneic anti-donor antibodies directed against T cells was significantly associated with an unfavourable graft prognosis. Patients with post-transplant anti-donor B cell antibodies had lower (but not significantly) graft survival rates. These findings provide additional evidence for a crucial role of anti-donor antibodies in kidney graft outcome.

Introduction

Immediate damage to human renal allografts caused by preformed donor specific antibodies and resulting in hyperacute graft rejection was described between 1966 and 1969 [1,2]. Until recently a negative crossmatch between recipient serum and donor lymphocytes was therefore an absolute requirement for renal transplantation. In 1976, Ettenger et al [3] reported that a positive crossmatch against donor B lymphocytes was not associated with early irreversible graft rejection. This result was later confirmed by other authors [4,5]. The role of pre- and post-transplant B cell antibodies has been studied during the past three years. It is now generally accepted that a positive B cell crossmatch is not an absolute contraindication to transplantation. Whether patients receiving a transplant with a positive B cell crossmatch really do better than those with a negative crossmatch has been unclear up to now. A controversial topic is the significance of post-transplant anti-donor B and T cell antibodies. It was shown by some laboratories that the development of B cell antibodies was associated with a higher rate of graft
rejection [6–8]. Others were unable to find any adverse effect on graft outcome [9,10]. Thus, the precise role of the different types of pre- and post-transplant antibodies must be definitively determined. To contribute to this question we analysed kidney graft survival in relation to whether the recipient antibodies are B or T cell reactive, and also whether they reacted optimally at 4°C or at 37°C.

Patients and methods

The study group comprised 183 recipients of cadaver kidney transplants, including 7 second transplants. Standard immunosuppressive therapy consisted of azathioprine and prednisolone. During graft rejection episodes the patients received high doses of methylprednisolone (1.0g) intravenously. Serial serum samples were taken from each patient before and after transplantation, deep-frozen, and tested against specific donor B and T cells at different temperatures in the microcytotoxicity assay. Before use, an aliquot of each serum was exhaustively absorbed on pooled human platelets. Absorption was performed twice by incubation of 1ml of recipient serum with an equal volume of packed platelets for 1hr at 22°C and 1hr at 4°C. In this procedure anti-HLA-ABC antibodies are completely removed as assessed by parallel testing with T lymphocytes; B and T cells of the kidney donor (spleen) were separated over nylon wool columns and frozen in liquid nitrogen at −180°C on the day of transplantation. The actuarial transplant survival rates were computed according to the method of Merrell and Shulman [11]. The statistical significance was calculated by the log rank test. Non-immunological transplant failures were not excluded from analysis.

Results

We examined 183 patients with negative T cell cross-matches. Forty-four of them had pretransplant anti-donor B cell antibodies (B-Ab); 19 patient sera reacted only at 4°C (cold B-Ab) whereas 25 sera reacted optimally at 37°C (warm B-Ab). Kidney transplant survival rates of patients with cold anti-donor B-Ab were higher than those of patients with warm B-Ab (Figure 1), although the differences were not statistically significant. Patients with cold B-Ab also had higher transplant survival rates at 1 yr (73%) than patients with no pre-transplant antibodies (54%). One year transplant survival of patients with warm B-Ab was slightly lower (48%) than in the antibody-negative group.

Since a positive B cell crossmatch may be caused by weak HLA-ABC antibodies, aliquots of all sera were exhaustively absorbed by pooled platelets and tested against donor B lymphocytes. In nine cases cold B-Ab were removed by absorption with platelets, indicating that the sera contained HLA-ABC antibodies. Five out of nine transplants (55%) functioned at 1 yr in those patients. Patients with cold B-Ab (unabsorbable by platelets) had a 1 yr transplant survival rate of 90% (9 out of 10 transplants). Patients with warm B-Ab absorbable or non-absorbable by platelets had comparable graft survival rates (53% vs. 47%). From these results, it seems that many of the patients with pretransplant cold B-Ab which cannot be removed by absorption with platelets may have a higher graft survival. In patients
with preformed warm B-Ab (absorbed by platelets or not), graft survival seems to be lower than in antibody-negative patients.

In Figure 2, the outcome of 181 kidney transplantation is shown in relation to anti-donor antibodies occurring or persisting after transplantation. Best results were found in recipients without detectable antibodies (graft survival 61% at 1 yr). The presence of B-Ab resulted in lower graft survival rates (53% at 1 yr, P = n.s.). Transplant survival rates of patients with anti-T cell antibodies (T-Ab) were poorest (41% at 1 yr; p < 0.01).

In a further analysis, the patients with post-transplant B cell antibodies were subdivided into those with cold or warm antibodies as well as into those with B-Ab absorbable or not absorbable by platelets. In the cold B-Ab group, 1 yr graft survival was 68% as compared to only 43% in the warm B-Ab positive patients (not statistically significant). In patients with or without platelet absorbable B-Ab, no marked difference of graft survival rates was found (49% vs. 56% at 1 yr). Because the numbers were too small, a similar analysis was not performed for the different types of post-transplant T-Ab.
Figure 2. Actuarial survival rates of cadaver kidney transplants in recipients with post-
transplant anti-donor antibodies (B-Ab = B cell antibodies, T-Ab = T cell antibodies) 
and in recipients without detectable antibodies (no Ab)

Discussion

There is some controversy with regard to the significance of B cell antibodies in 
kidney transplantation [3–10]. Our results confirm previous reports that suc-
cessful transplantation can be carried out in spite of a positive B cell crossmatch 
[3–5,9,10]. However, it is doubtful whether such antibodies have a protective 
effect on graft survival. In several studies, Iwaki et al [12] and Ayoub et al [13] 
have shown that patients who have cold antibodies (mostly autoreactive) have a 
higher kidney transplant survival rate than patients with no preformed cytotoxins. 
There is no knowledge about the stimulus for the development or the specificity 
of such autoreactive antibodies. This type of antibody seems not be be induced 
by transfusion or pregnancy since it can be found in non-transfused male patients. 
One possible stimulus for such antibodies might be previous viral infections. It is 
also not known whether the corresponding antigens are present on kidney tissue. 
In vitro studies have shown that these autoreactive antibodies react optimally at
low temperature, indicating that they may not be active in vivo. It is the more surprising that cold antibodies may enhance graft survival [12,13]. In our material, too, a higher graft survival rate was to be found in patients with such antibodies. Data have been presented showing that cold cytotoxins are formed in response to various immunological stimuli, belong to the IgM class, and are directed against cell-bound immunoglobulins; in the crossmatch situation, they are directed against IgM bearing donor B lymphocytes. The more generalised function of this type of antibodies reacting with autologous and allogeneic B cells optimally in the cold is thought to be immunoregulation [13]. We have shown that the occurrence or persistence of antibodies against donor T lymphocytes was significantly associated with impaired graft function. Patients with post-transplant anti-donor B cell antibodies also had lower graft survival rates. However, especially with respect to B cell antibodies, it is necessary to distinguish between allogeneic antibodies reacting optimally at warm temperatures and between cold antibodies, mostly autoreactive. This distinction is important because only the allogeneic antibody group had an unfavourable graft survival. These results might be an explanation for different findings on the influence of post-transplant B cell antibodies [6–10]. The significance of the different types of pre-and post-transplant antibodies in kidney transplantation must be determined by further studies. In conclusion, our findings provide additional evidence for a crucial role of anti-donor antibodies in kidney transplantation.

References

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