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Multicentre trial of ABO-incompatible kidney transplantation

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Japanese Biosynsorb ABO-incompatible kidney transplant study group

Abstract. A multicentre study of ABO incompatible kidney transplantation using Biosynsorb was started in Japan in November 1989. A total of 51 cases were registered comprising 23 cases of A incompatibility, 26 cases of B incompatibility and two cases of AB incompatibility. The removal of antibodies (IgG and IgM) was carried out using Biosynsorb in 16 cases, plasmapheresis in four cases and use of both combined in 31 cases. The treatment using Biosynsorb was repeated 3.4 times on average. Serum titres of anti-A (IgG and IgM) antibodies decreased to 4.9 ± 5.0 and 2.7 ± 1.7 and for anti-B titres decreased to 2.8 ± 3.5 and 2.4 ± 3.2. Rejection was found in 33 cases: hyperacute one, accelerated acute five, and acute 27. In two cases rejection was developed concomitantly with a steep elevation in antibody titres. Three patients died, two with functioning grafts. Eight grafts were lost. Patient and graft survivals at 2 years were 94.1% and 84.3%, respectively. From these results it is concluded that: 1. Biosynsorb and plasmapheresis are effective in removing anti-A and anti-B antibodies; 2. graft and patient survivals are similar to those in ABO compatible cases; 3. anti-A and anti-B titres less than 16 are recommended at the time of transplantation; 4. anti-A and anti-B titres higher than 128 may be considered as a risk factor for rejection in the early stages after transplantation.

Key words: ABO-incompatible kidney transplantation – Anti-A and anti-B antibodies – Plasmapheresis – Adsorption of antibodies – Biosynsorb

By the end of 1990, 7740 kidneys had been transplanted in Japan. Living donors were used in 28.2% of these cases. Despite our efforts to promote organ donation, the number of transplantations using cadaveric kidneys has not increased to satisfy the demand of 15000 patients on the waiting list. In such a situation we are obliged to use family donors. Accordingly, we often encounter ABO-incompatible potential donor-recipient combinations with no other choice.

Since the introduction of plasmapheresis and the Biosynsorb adsorbent column (Chembiomed, Kawasmi Laboratories) [4] to remove anti-A, and anti-B antibodies, kidney transplantation across the ABO barrier, which hither to was considered very risky, has become a feasible operation.

A multicentre trial including 12 centres was started in Japan in November 1987 and, by the end of December 1990, 51 cases had been registered. This paper describes data obtained from these 51 cases along with the effects and side-effects of Biosynsorb.

Materials and methods

Patients

Patients enrolled in this study were 36 males and 15 females and their average age was 32.6 ± 2.6 years. They were divided into three categories: A-incompatible 23 cases (A to O, 13; A to B, 5; AB to B,

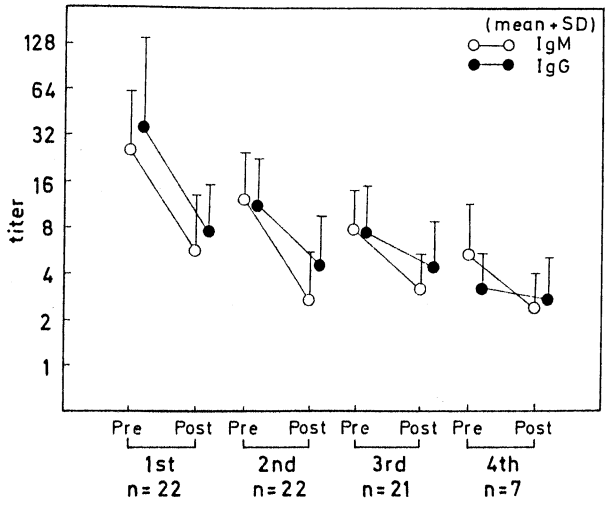

Fig. 1. Average reduction in anti-A antibody for each treatment

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5); B-incompatible 26 cases (B to O, 17; B to A, 3; AB to A, 6); and AB-incompatible, two cases. Nine grafts were donated from fathers, 29 from mothers, five from siblings, two from husbands and six from wives. The average mumber of HLA mismatches was 2.4 ± 1.3 and the number of one-way MLR stimulation indices was 19.5 ± 20.1.

Removal of anti-A and anti-B antibodies

All patients were treated with either Biosynsorb and/or double filtration plasmapheresis (DFPP) [1], a method using double filters specially designed to retrieve albumin. Biosynsorb-A was used to remove anti-A and Biosynsorb-B to remove anti-B antibody. The treatment was started 7 days prior to transplantation and repeated three or four times finishing on the day of, or one day before, the operation.

Blood flow and total volume of plasma treated were measured. Titres of anti-A (IgG and IgM) and anti-B (IgG and IgM) antibodies were examined using indirect Coombs, Bromelin and saline test methods along with complement (CH50, C3, C4, C3a and C5a), blood cell count and blood chemistry before, during and after the procedure.

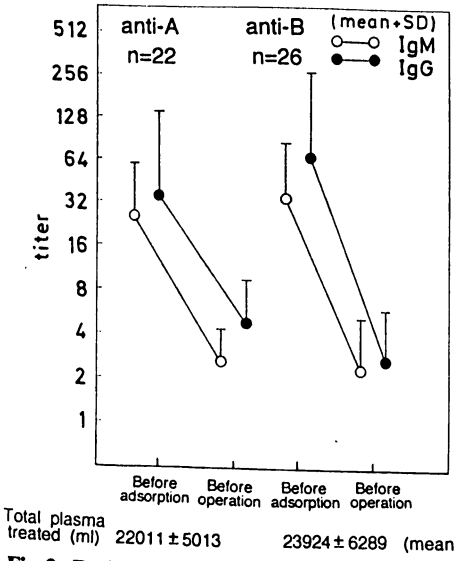

Fig. 2. Reduction in anti-A and anti-B antibody titres before adsorption and before surgery

Immunosuppression

Cyclosporine (CsA), azathioprine (Az) and steroid, were used as the basic immunosuppressive drugs and antilymphocyte globulin and deoxyspergualin were added in the majority of cases. Pulse therapy with methylprednisolone (500 mg/day) for 2–3 days and 5 mg/day of muromonab CD3 for 10 days were used during rejection.

Operation

Kidney transplantation was done using the standard method described by Merrill et al. [7], and the spleen was removed in all except two cases.

Patient and graft survivals

Survivals of patient and graft were evaluated using the Kaplan-Meier method and compared with those obtained from the contemporaneous Japanese kidney transplant registry.

Results

Removal of anti-A and anti-B antibodies

Out of 51 cases, 16 were treated exclusively with Biosynsorb, and 31 with combined Biosynsorb and DFPP. In four cases the treatment with Biosynsorb was stopped within 10 min because of hypersensitivity reactions manifested as chest pain and a fall in blood pressure. These patients were switched to DFPP thereafter.

For the removal of anti-A antibody, 72 sessions of adsorption were carried out for 22 cases. The average volume of plasma processed was 6725 ml. Titres of IgG and IgM antibodies decreased from 17.4 ± 60.3 to 5.3 ± 5.9 (reduction, 43.8%), and 15.1 ± 22.8 to 4.0 ± 4.5 (reduction, 59.0%), respectively.

For the removal of anti-B antibody, 89 sessions of adsorption were carried out for 26 cases. The average vol-

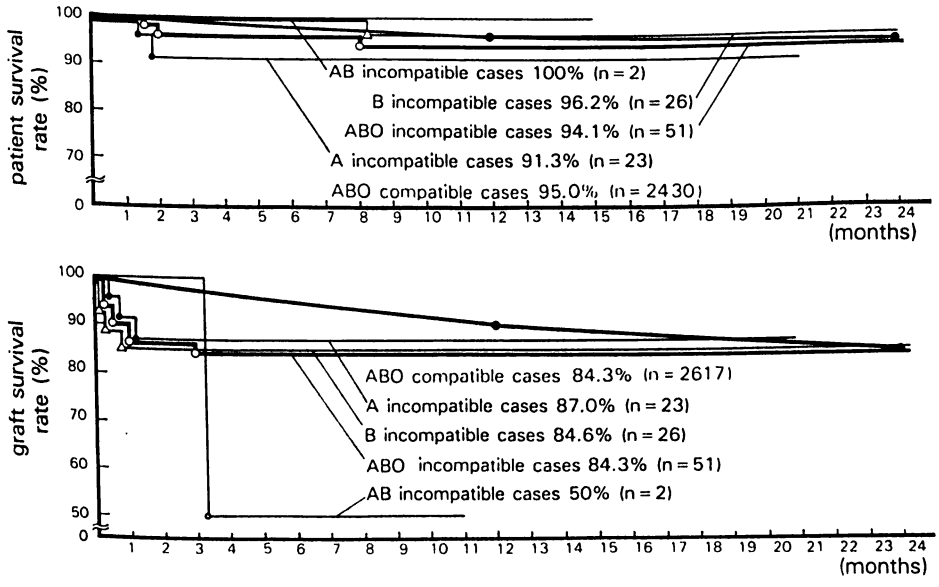

Fig. 3. Patient and graft survival rates (Kaplan-Meier method). ABO incompatible cases were obtained from the Japanese kidney transplant registry

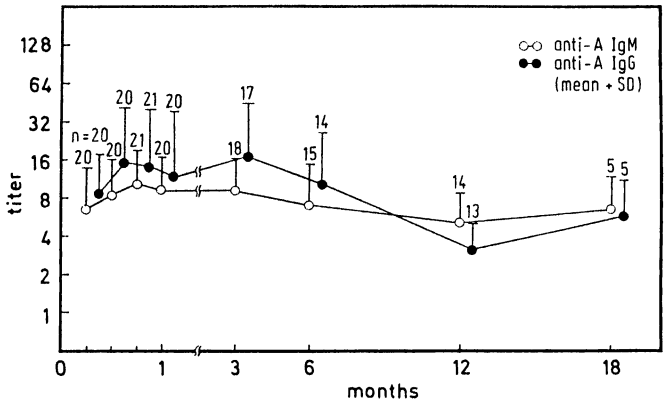

Fig. 4. Levels of anti-A antibody titres after transplantation

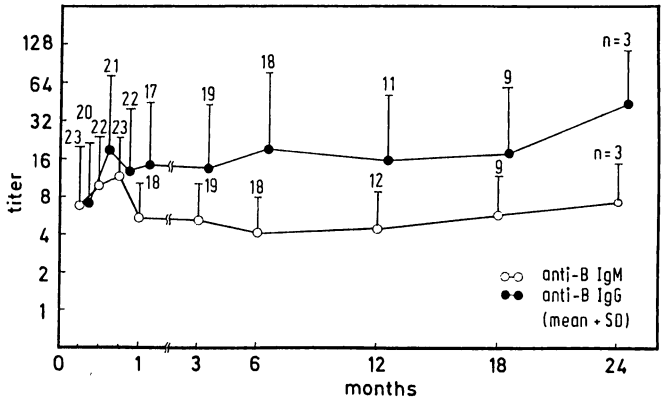

Fig. 5. Levels of anti-B antibody titres after transplantation

ume of plasma processed was 6952 ml. Titres of IgG and IgM antibodies decreased from 33.1 ± 115.9 to 7.5 ± 28.3 (reduction, 66.4%) and 17.6 ± 32.7 to 3.3 ± 4.1 (reduction, 73.3%).

The average preoperative adsorption was 3.4 times and total volume of plasma processed was 23029 ml for each patient. By repeating the treatment, titres of anti-A IgG and IgM antibodies decreased from 37.0 ± 107.1 to 4.9 ± 5.0 and 26.7 ± 35.8 to 2.7 ± 1.7, respectively, and the titres of anti-B IgG and IgM antibodies decreased from 69.0 ± 202.1 to 2.8 ± 3.5 and 36.2 ± 54.3 to 2.4 ± 3.2, respectively, by the time of transplantation (Figs. 1 and 2).

There were no significant changes in erythrocyte count and level of albumin. A significant change ($P < 0.05$) was observed in the levels of IgG, IgA, IgM, C3a and C5a.

Transplantation and postoperative course

In all cases transplantation surgery was successful. In two cases splenectomy was not performed. Hyperacute and accelerated acute rejection developed in one and five cases, respectively, and in two of the latter, the graft was rejected. Acute rejection developed in 27 cases and in six of these, the graft was rejected. Two of the latter were not splenectomized. In the remaining 21 cases no rejection was found.

Blood type incompatibilities of those 8 cases who had their graft rejected were: A-incompatible, three; B-incompatible, four; and AB incompatible one. No chronic rejection was found in any of the 51 cases.

Three patients died on the 48th, 55th and 244th postoperative day from pancreatitis, brain haemorrhage, and malignant lymphoma, respectively. In two cases, patients died with functioning grafts, while the patient who died of brain hemorrhage was on dialysis after having his graft removed on the 29th postoperative day. Other postoperative complications observed were: cytomegalovirus infection and peritonitis, four cases each; pancreatitis, three cases; urinary tract infection, two cases; and haemorrhagic cystitis, leukopenia, atelectasis, malignant lymphoma, and brain haemorrhage, one case each.

During the observation period of two years, average serum creatinine levels remained around 1.5 mg/dl in both A-incompatible and B-incompatible cases.

As shown in Fig. 3, patient survivals for total cases, and A-, B-, and AB-incompatible cases were 94.1%, 91.3%, 96.2% and 100%, respectively, and graft survivals were 84.3%, 87.0%, 84.6% and 50%, respectively.

Serum levels of anti-A and anti-B antibody

The anti-A and anti-B antibody titres were followed for 2 years. As shown in Fig. 4 the average levels of IgG and IgM anti-A antibody titres fluctuated between 4 and 16, and anti-B titres showed similar fluctuation between 4 and 32 during the observation period. Among five patients who had their grafts rejected within 1 month after transplantation, two showed extremely high antibody titres (IgG, 1024 and 2048; IgM, 1024 and 512), while two patients who had their kidney rejected after 1 month showed no change in antibody titres. The adsorption using Biosynsorb after transplantation was performed 32 times for 11 cases to treat rejection and/or to lower the level of antibodies.

Discussion

There are several measures to remove anti-A and anti-B antibodies. Adsorption using Biosynsorb and plasmapheresis are most commonly used. In this study both of the methods proved to be safe and effective as described by Alexandre et al. [2] and Bannet et al. [3]. The advantage of the former is that no special substitution fluid is necessary. However, the column is very expensive and there is also the risk of hypersensitivity reactions. Plasmapheresis has the potential risk of viral transmission by infused plasma. DFPP, which was introduced to minimize the volume of substitution fluid, proved to be safe and effective. While globulin removed in one session is equivalent to that contained in 5 l of plasma, only 1 l of 7.5% albumin solution was necessary to compensate for the deficiency. There is no difference between A- and B-incompatible cases with regard to the effectiveness of antibody removal.

Since our study had no control group, graft and patient survivals were compared with those obtained from the Japanese registry of kidney transplantation. As shown in Fig. 3, the results obtained in ABO-incompatible cases were similar to those of ABO compatible cases.

There were two cases transplanted without splenectomy. The fact that both of the grafts were rejected within 2 weeks suggests the importance of splenectomy in ABO-incompatible transplantation.

Based on the fact that, in this study, no kidney was rejected in a hyperacute manner, serum levels of IgG and IgM antibodies less than 16 could be considered acceptable to perform ABO-incompatible transplantation. There is controversy as to whether elevation of anti-A and anti-B antibody plays of role in the process of rejection [5, 6]. In our series there were two kidneys rapidly rejected within a week after transplantation concomitant with elevation in IgG and IgM antibody titres. This finding suggests that elevated anti-A and anti-B antibodies triggers and/or enhances rejection crises, particularly in the early stages of transplantation.

It can be concluded that ABO-incompatible transplantation is acceptable if no other donor is available. Graft and patient survivals are nearly equal to those of ABO-compatible cases. For a successful outcome, preparation including splenectomy and reduction of anti-A and anti-B antibody titres below 16 at the time of transplantation is recommended, along with careful monitoring of antibodies and kidney function.

References

1. Agishi T, Kaneko I, Hasuo Y, Hayasaka Y, Sanaka T, Ota K (1980) Double filtration plasmapheresis. Trans Am Soc Artif Intern Organs 26: 406–411
2. Alexandre GPJ, Squifflet JP, Bruyere MD, Latinne R, Reding R, Gianello P, Carlier M, Pirson Y (1987) Present experiences in a series of 26 ABO-incompatible living donor renal allografts. Transplant Proc 19: 4538–4542
3. Bannett AD, McAlack RF, Raja R, Baquero A, Morris M (1987) Experiences with known ABO-mismatched renal transplants. Transplant Proc 19: 4543–4546
4. Bensinger WI, Baker DA, Buckner CD, Clift RA, Thomas ED (1981) Immunoadsorption for removal of A and B blood-group antibodies. N Engl J Med 304: 160–162
5. Chopek MW, Simmons RL, Platt JL (1987) ABO-incompatible kidney transplantation: initial immunopathologic evaluation. Transplant Proc 19: 4553–4557
6. McAlack RF, Bannett AD, Raja R, Kim P, Romano E, Lauzon G (1987) Delayed hyperacute rejection in an ABO-incompatible renal transplant. Transplant Proc 19: 4558–4560
7. Merrill JP, Murray JE, Harrison JH, Guild WG (1956) Successful homotransplantation of the human kidney between identical twins. JAMA 160: 277–282