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Case Study

ABO Incompatible Kidney Transplantation- A review with a perspective from a center in India

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ABSTRACT

ABO incompatible kidney transplantation is performed all over the world in order to increase the donor pool and reduce the waiting time for kidney transplantation. The success of such transplantation depends on the desensitization at the time of transplantation. Although in the immediate post operative period more antibody mediated rejections are seen the long term outcome is excellent comparable to the regular kidney transplantation. In a country like India, infections are a major problem related to excessive immunosupression. This article describes the present state of art in ABO incompatible kidney transplantations and the experience of a center from South India where 35 patients have undergone such transplantation.

1. Introduction

The demand for kidney transplantation is ever growing all over the world. Many centers are not able to accept related kidney donors due to blood group incompatibility. The waiting period for deceased donor transplantation is often very long, preventing patients from undergoing transplantation. Hence it becomes essential to increase the donor pool. ABO incompatible kidney transplantations (ABOi KT) are getting popular all over the world with excellent results**[1-4]**. Japan leads the foremost with more than 1800 such transplantations. It almost accounts to 30% of all living donor kidney transplantation in Japan**[5]**. Successful ABOi KT's have been reported in our country also**[6,7]**. There has been an increase in such transplants in the last decade both in the United States and Europe**[8]**.

Tracing the history of ABOi KT, the initial attempt was made by Chung et al in 1955**[9]**. In their experience, 8 out of 10 grafts were lost in the immediate post operative period. In 1987, Alexandre *et al.* introduced an effective desensitization protocol, whereby he could achieve success in such kidney transplantations**[10]**. The protocol included pre transplant plasmapheresis, triple immunosuppression including Cyclosporine and Splenectomy. In 23 recipients, he reported a 1 year graft survival of 75% and recipient survival of 88%. In the absence of deceased donor transplantation, Japan reported more than 1000 cases till 2005**[11]**. It almost reached 14% of all living transplantation and now it is routinely being offered in many centers. At present ABOi KT constitute 30% of all living transplantation in Japan**[12]**. The increase has been dramatic after Splenectomy was given up in the protocol for desensitization. Splenectomy had a 25% mortality and long term susceptibility to infections**[13]**. The success of ABOi KT essentially depends upon desensitization. There are different protocols followed all over the world. They essentially consist of the following.

A. Monitoring of anti-A and anti-B titers

Three methods are available to estimate the titers**[14]**.

(i). Conventional tube method, which is the least accurate.

(ii). The automated Gel Card method.

(iii) Flow cytometry estimations. The latter two are very sensitive and more reproducible. According to Cheng *et al.* the conventional tube method is often $1/4^{th}$ of the Gel and Flow cytometry methods**[15]**. Many centers have different cut-off for the titers ranging from 1:4 to 1:32. The conventional tube method is almost given-up.

B. Removal of antibodies

The anti-A and anti-B antibodies are removed successfully by 3 methods.

(i). Conventional plasma exchange – This is the easiest and the least expensive. But it is non selective and results in loss of coagulation factors, hormones etc leading to higher bleeding complications**[15]**. The replacement can be in the form of albumin or plasma.

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(ii). DFPP (Double Filtration Plasmapheresis)[16] – This has two filters and the first one separates the cells from plasma and the second filter is more selective separating out the immunoglobulin from low molecular weight proteins. This procedure has less bleeding complication and requires fewer albumins for replacement. Of course it requires a special machine and is more expensive.

(iii). Immunoadsorption (IA)[17] – This involves separating out of plasma and passing out through specific anti-A, anti-B columns (Glycosorb) and returning the plasma back to the patient. This is the most efficient method of removal of antibodies and the most expensive.

C. Intravenous immunoglobulin (IVIG)

Almost all the centers give either low or regular dose of IVIG following each plasma exchange[18]. The IVIG place the role in down regulation of the antibody mediated immune response. It inhibits the CD-19 expression on the activated B-cell as well as that of the complement and allows reactive T-cell. It blocks the Fc receptor on the mononuclear phagocyte. The effect of IVIG will persist for several months after administration. Two of the major Japanese centers Tanabe and Uchida do not use IVIG.

D. Anti CD-20 monoclonal antibody (Rituximab)

Rituximab has replaced splnectomy in ABOi KT[19]. It directly inhibits B-cell proliferation and induces cellular apoptosis through the binding of complement. It is considered a chemical splenectomy because of its potent B-cell ablation. Its effect is seen in 72hrs and lasts several months. Majority of the center use single dose of Rituximab a week to 2 prior to kidney transplantation. The dose used is also variable. Majority give 375 mg/m^2[18]. Tanabe has shown the 200 mg of Rituximab is as effective as the conventional dose in B Cell depletion both in the periphery and spleen[20]. The long term outcome of patient who received the conventional dose and the reduced dose of Rituximab has not been different[21]. Flint and Montgomery et al have shown successful transplantations without using Rituximab only with plasma exchange and IVIG. They reported a graft survival rate of 88.7%[22].

E. Immunosuppression

Steriods, Mycophenolate, Calcineurin inhibitors and induction with Basiliximab or ATG is the standard protocol. Tanabe has shown that Tacrolimus has an improved graft survival over Cyclosporine administration[19].

F. Post operative monitoring

Post operatively, the titers are monitored for varying periods by different centers. As a routine very few centers give plasmapheresis at present. A jump in titer more than 1:16 may warrant intervention in the form of plasmapheresis[18]. The titers do not necessarily correlate with the renal functions. Impairment in renal function requires immediate intervention[20].

Antibody Mediated Rejection (ABMR)

ABMR is being primary cause of graft loss after ABOi KT. Recent studies have shown an incidence between 17.9 up to 30% of ABOi KT's[23-25]. The greatest of ABMR is seen between 2 to 7 days and rarely occurs after 1 month. The critical period seems to be the first two weeks, during which accommodation is established[26]. Accommodation is a process where in spite of antibodies, the graft has normal function. Often C4D is present in the graft with normal function and structure. The mechanism of accommodation is not well understood. Often ABMR is precipitated by bacterial infections since bacteria share the blood group antigens. The diagnosis to ABMR has to be rapid. Any drop in urine output warrants an immediate biopsy. The standard treatment for ABMR is plasmapheresis followed by low dose IVIG on alternate days till renal function improves[27]. In refractory cases, Rituximab or Bortezomib has been tried[28]. Splenectomy has also been used as a rescue treatment in severe ABMR[29].

Clinical outcomes of ABOi KT

Several centers have reported excellent graft and patient survival in the short term. Montgomery reported 1 year patient and graft survival of 96.3% and 98.3% respectively in a cohort of 60 patients[30]. Oettl *et al.* demonstrated 100% survival of both patients and graft at 1 year[31]. The long term outcomes have also been equivalent to regular kidney transplantations. Tyden et al reported a graft survival of 97% for ABOi KT as compared to 95% of compatible kidney transplantations in a 5 year follow up[32]. Tanabe reported the outcome of 850 ABOi KT's performed in Japan between 1989 and 2005. The 5 year graft survival was 79% with patient survival of 90%[19]. Montgomery reported patients and graft survival of 89% at John Hopkins hospital[30]. Fuchinoue et al reported a 5 year graft survival 100%[33].

Our center experience

We started our ABOi KT in MIOT Hospitals, Chennai, India in 2009. So far 35 patients have undergone such transplantations. All transplants were worked up in similar fashion to regular kidney transplantation. Preconditioning was done as per Tanabe's protocol [34]. A single dose of 200 micrograms Rituximab was given 7 days prior to kidney transplantation. Patients were put on a triple immunosuppression consisting of Tacrolimus 0.1 mg/kg body weight, Mycophenolate 1 gm twice a day and Predinsolone 10 mg/day. The Tacrolimus levels were adjusted to 10-12 ng/ml. Alternate day plasma exchange was carried out at 40 ml/kg body weight after dialysis. Albumin with saline was used as replacement fluid. Anti-A and Anti-B titers were estimated on a daily basis using conventional Tube method initially and subsequently by Gel Card method. Transplantation was carried out if the titers dropped to 1:16 or less (Gel Card Method). Basiliximab was given as induction therapy. Post operatively the titers were monitored on a daily basis for the first 2 weeks. After 2 weeks, the steroid dose was brought down to maintenance dose of 5 mg, Tacrolimus levels to 5-10 ng/ml and 1.5 gm of Mycophenolate per day. After one month, the Tacrolimus level was brought down to 3-5 ng/ml.

The very first patient who had ABOi KT had hyperacute rejection on table. This put our programme back by about 1 year and we could restart regularly only from 2010. Including the first patient, 6 had Antibody Mediated Rejection (ABMR).

Out of these, 2 of the grafts could be salvaged. 2 patients were lost out of the 35, one due to bleeding complication in the first post operative week and other due to pulmonary aspergillosis 3 months after successful transplantation with normal functioning graft. 3 of the patients who lost their graft due to rejection have undergone successful re-transplantation with deceased donors subsequently. 30 patients are doing well. The follow-up period has been between 2 to 60 months. The average serum creatinine is 1.2 mg % with the range between 0.8 and 1.8. Out of the 35 patients, 21 were male and 14 females. 5 were diabetic. 8 patients had parents as donors, 16 as spouses and 2 unrelated (Mother-in-law and Brother-in-law). The transplants have been across various blood groups with maximum number of patients being 'O' (22), 'A' (9) and 'B' (4). 2 patients developed recurrent urinary tract infection which could be treated successfully. 1 patient who had CAPD for 10 years could undergo successful transplantation because we started the ABOi KT programme. 3 were children less than 16 years of age. ABMR occurred in 6 patients in the first week of transplantation itself. 2 of them had hyper acute rejection and the graft had to be removed. 2 patients developed ABMR precipitated by UTI. In spite of plasmapheresis and IVIG therapy, the grafts were lost. In 2 other patients, the ABMR reversed successfully after the initiation of plasma exchange and IVIG. This was because we picked up the rejection very early due to our previous experience and initiated the patients on therapy without waiting for the biopsy results. It is essential that time is not lost to initiate therapy to save the graft. The approximate cost for ABOi KT in our center is USD 15000 for 2 week hospitalization including plasma exchange, induction therapy etc.

Conclusion

Summarizing, ABOi KT has come to stay all over the world. Very few centers in India offer this on a regular basis. Sporadically many centers have done such transplantations successfully. The biggest obstacles are fear of increased infections, increased ABMR and increased cost. Our experience with 35 patients has shown that ABOi KT can safely be accepted as a line of treatment in a country like India.

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