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REVIEW ARTICLE

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# Intravenous immunoglobulins and transplantation for patients with anti-HLA antibodies

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**Abstract** Transplantation for patients possessing allo-antibodies against HLA antigens can be delayed for years, and, once the graft has been transplanted, its survival is significantly reduced. We and others have shown that administration of intravenous immunoglobulins (IVIgs) can induce a profound and sustained decrease in the titres of the anti-HLA antibodies, thus greatly enhancing the chances of those patients to obtain a transplant. In a number of cases, pre-treatment sera contained anti-donor antibodies that disappeared after IVIg administration. A similar approach, combining plasmapheresis and low-dose IVIgs, has shown similar results and has been successfully applied to ABO-incompatible transplantations. Patient and graft survival are excellent, despite a rather high rate of rejections, most notably humoral ones. These protocols thus demonstrate that the presence of anti-donor antibody, once an absolute contra-indication to transplantation, can, nowadays, be considered as an immunological hurdle that can be managed through appropriate immunological manipulation.

**Keywords** IVIgs · Organ transplantation · Anti-HLA antibodies · Humoral rejection · Anti-donor antibodies · Immunomodulation

## Introduction

Up to 30% of patients waiting for a renal allograft are immunised, that is they possess in their sera antibodies directed against allogeneic HLA molecules. Transplantation for such patients is hampered by the need for a compatible organ to be found, which does not harbour any of the HLA molecules recognised by the patient's antibodies. Thus, the waiting time for those patients extends frequently to more than 3 years. Indeed, according to the French Transplant Registry, after 5 years of waiting, only one third of those patients have received transplants [1]. Once they have received grafts, these patients are at risk, with more rejections and a lower graft survival rate than naïve patients.

It is thus important that a strategy be devised for those patients to reduce their waiting time and decrease the risk of rejection post-transplantation by elimination of their allo-antibodies. A number of protocols in the past have used plasma exchanges [2] or immunoadsorption techniques coupled with immunosuppressive agents [3], with variable success and at the price of important side effects.

We report here the experience of our centre and others of using intravenous immunoglobulins (IVIgs) alone or in combination with plasmapheresis in transplantation in such patients.

## Anti-HLA antibodies and rejection

The presence of antibodies of the IgG isotype, directed against the HLA class I molecules borne by the graft, correlates well with episodes of severe acute rejections

and ultimate graft loss [4]. The existence of these antibodies is demonstrated by a technique called "crossmatch", in which the serum of the recipient is incubated with lymphocytes from the donor, and the potential binding revealed, either through cytotoxicity with rabbit complement or through flow cytometry using a secondary antibody. The sensitivity of the cytotoxic assay may be enhanced by use of an anti-human Ig antibody as a secondary reagent (AHG-enhanced crossmatch). The positivity of a classical cytotoxic T cell IgG crossmatch is an absolute contra-indication to transplantation. However, a positive crossmatch by other techniques, such as flow cytometry, does not rule out transplantation, as it is only associated with a higher frequency of rejection, with little, if any, deleterious effect on graft survival [5, 6].

More recently, significant advances in the detection of these antibodies have been achieved. Patients with a negative standard crossmatch who demonstrate anti-HLA antibodies by a new ELISA technique experience a significantly higher frequency of acute rejections [7, 8], with more severe histological lesions, most notably vasculitis [9]. Graft survival is then inferior in this population of patients [10]. This implies that, aside from the well-known T cell-mediated rejection mechanisms, antibodies do play an important role in rejection and may be primarily responsible for the vascular lesions. Indeed, a cardiac transplantation under sub-optimal cyclosporine treatment is rejected much faster in normal mice than in knock-out mice unable to synthesise antibodies [11]. Recently, the use of these new techniques to detect anti-HLA antibodies have led to the concept that chronic rejection is almost invariably preceded by the appearance of antibodies [12] and is most probably a consequence of allo-immunisation [13].

The presence of anti-HLA antibodies in a patient waiting for a renal allograft thus induces both a longer waiting time, due to a number of incompatible organs, and worse survival of the graft, through a higher frequency of acute rejection and an increase in chronic graft dysfunction leading ultimately to graft loss.

## IVIg

IVIgs are commercial preparations of immunoglobulins of the G isotype (IgG), made from plasma pools obtained from thousands of healthy donors. IVIgs consist of 97% IgG molecules, with a ratio of the IgG1, IgG2, IgG3 and IgG4 isotypes comparable to human sera. Most preparations contain monomers or dimers with less than 5% of aggregated IgG, very little F(ab')2 fragments and only traces of IgM and IgA. At high concentration, aggregation can occur, which may cause untoward effects during infusion. This can be circumvented by the use of three different treatments: enzymatic treatment by pepsin with or without acidic conditions, chemical treatment (alkylation/reduction, propiolactone) or fractionation (PEG precipitation, adsorption on a DEAE sepharose column) [14]. According to the type of preparation, soluble HLA molecules may be present [15].

IVIg administration has proven efficacy in a number of auto-immune diseases such as idiopathic thrombocytopenic purpura, haemolytic anaemias, auto-immune neutropenias (reviewed in [16]).

Clinical experience of the use of IVIg to regulate allo-antibodies has been much more limited and mostly restricted for years to allo-anti-platelet antibodies seen after multiple transfusions [17].

The immunological mechanisms responsible are diverse and probably disease specific. As opposed to monoclonal antibodies, IVIgs may act on numerous components of the immune system, either through their F(ab')2 fragments, harbouring two antigen-binding sites, or through their Fc fragments, which bind complement (C1q, C3b, C4b). Among these various mechanisms of action, some may have particular relevance in transplantation, as a prophylactic (P) or curative (C) treatment of rejection:

- Neutralisation of circulating antibodies, through idiotype-anti-idiotype interactions, as seen in autoimmune haemophilia (P, C) [18]
- Inhibition of secretion of cytokines and other soluble mediators, as seen in Kawasaki's disease (C) [19]
- Inhibition of the binding of complement fractions to their target cells, as seen in neuromuscular disorders (C) [20]
- Inhibition of B and T cell proliferation, with down-regulation of antibody synthesis, which has been demonstrated in vitro (P, C) [21, 22, 23]
- Inhibition of endothelial cell activation (P, C) [24]
- Inhibition of CD8 T cell cytotoxicity (P, C) [25]
- Increased apoptosis of B cells (P,C) [26]
- Inhibition of maturation and function of dendritic cells (P) [27]

## Anti-HLA immunisation

There are three different causes of allo-immunisation, namely transfusions, pregnancies or transplantations. This immunisation is much stronger (as determined by the antibody titer), polyreactive (number of HLA antigens recognised) and prolonged when, in the same patient, different causes of immunisation act together. Thus, after return to dialysis, fewer than 10% of the patients develop anti-HLA antibodies. If, at the time of transplantectomy, the patients receive a blood transfusion, this rises to 80% [28]. Likewise, only 5% of pregnant women become immunised, but if a blood

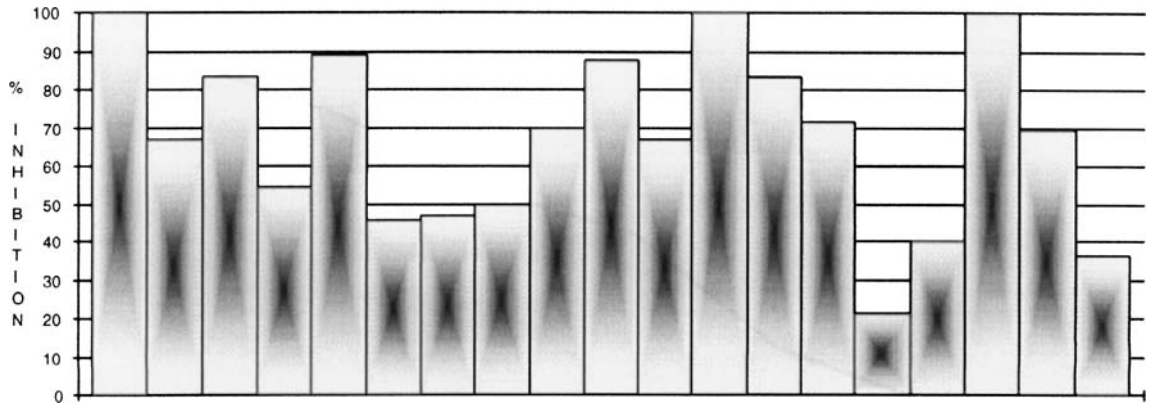


**Fig. 1** Percentage of inhibition of cytotoxicity (PRA) of sera by IVIgs

transfusion occurs, this rises to 50% [29]. Transfusions alone induce immunisation in only 10% of the patients. Thus, a strong and durable immunisation is nearly always the consequence of the association of transplantation and transfusions or pregnancy and transfusions.

As time goes by, this immunisation may:

- simply disappear
- persist
- disappear through an active phenomenon, the generation of anti-idiotypic antibodies [30]. Those anti-idiotypic antibodies inhibit the anti-HLA antibodies, blocking their cytotoxic effect [31], and are clearly associated with a better graft prognosis [32].

The clear demonstration that IVIgs contain such anti-idiotypic antibodies led us to investigate the potential interactions between IVIgs and anti-HLA antibodies [33].

## IVIgs and anti-HLA antibodies

### Laboratory data

We first tested the hypothesis that commercial preparations of IVIgs could block the cytotoxicity induced by anti-HLA antibodies. To this end we slightly modified the classical panel reactive antibody assay (PRA) by diluting the sera to be tested 1:2, either in phosphate-buffered saline, or in IVIgs (20 mg/ml). Lymphocyte target cells, provided by the local blood bank, were incubated with the sera, rabbit complement was added, and the lysis detected after addition of a vital dye. Results might be expressed either in absolute numbers (10/20, meaning that cells of half the donors had been lysed) or in percentage (50%).

Sera from 19 immunised patients were studied [34]. Results clearly showed that the addition of IVIgs significantly reduced cytotoxicity ($P < 0.0001$). Nearly half the sera had 50% or more inhibition of cytotoxicity, and only one serum showed no inhibition. The same assay was repeated with titrated sera (using the last dilution giving the same cytotoxicity as the neat serum). In this setting, all sera were inhibited by IVIgs (Fig. 1). It is of note that IVIgs alone never caused cytotoxicity and that the addition of IVIgs never led to an increase in cytotoxicity.

The precise mechanism responsible was investigated through analysis by flow cytometry of the binding of the antibodies to their target cells [33]. IVIgs do not appear to bind lymphocytes but inhibit the binding of the anti-HLA antibodies to the cells in a dose-dependant manner (Fig. 2). Equivalent results were found with F(ab')2 fragments of IVIgs, evoking the presence, among IVIg, of anti-idiotypic antibodies directed against the anti-HLA antibodies. This finding was confirmed, showing that a small fraction of IVIgs bind to F(ab')2 fragments of anti-HLA antibodies, and that this fraction has ten-times the inhibitory activity of intact IVIgs [35]. Moreover, this technique allows elimination of any potential soluble HLA molecule that could be present in the IVIgs [15].

### Clinical findings

We initiated a pilot study to ascertain the effects of IVIg infusion on the titre of anti-HLA antibodies. Ten patients were recruited. The inclusion criteria were:

- Patients on an active waiting list for transplantation
- With a stable titre during at least 6 months of IgG anti-HLA class I molecules
- Without transfusions or immunosuppressive therapy in the last 6 months
- After informed consent

Mean antibody titre pre-treatment was 50% (30 to 90). None of these patients had IgM anti-HLA or autoantibodies. The patients received 0.4 g/kg of IVIgs (Gamma-PEG, Pasteur-Mérieux, Lyon, France) during four consecutive dialysis sessions, and their anti-HLA titres were monitored by cytotoxicity during the

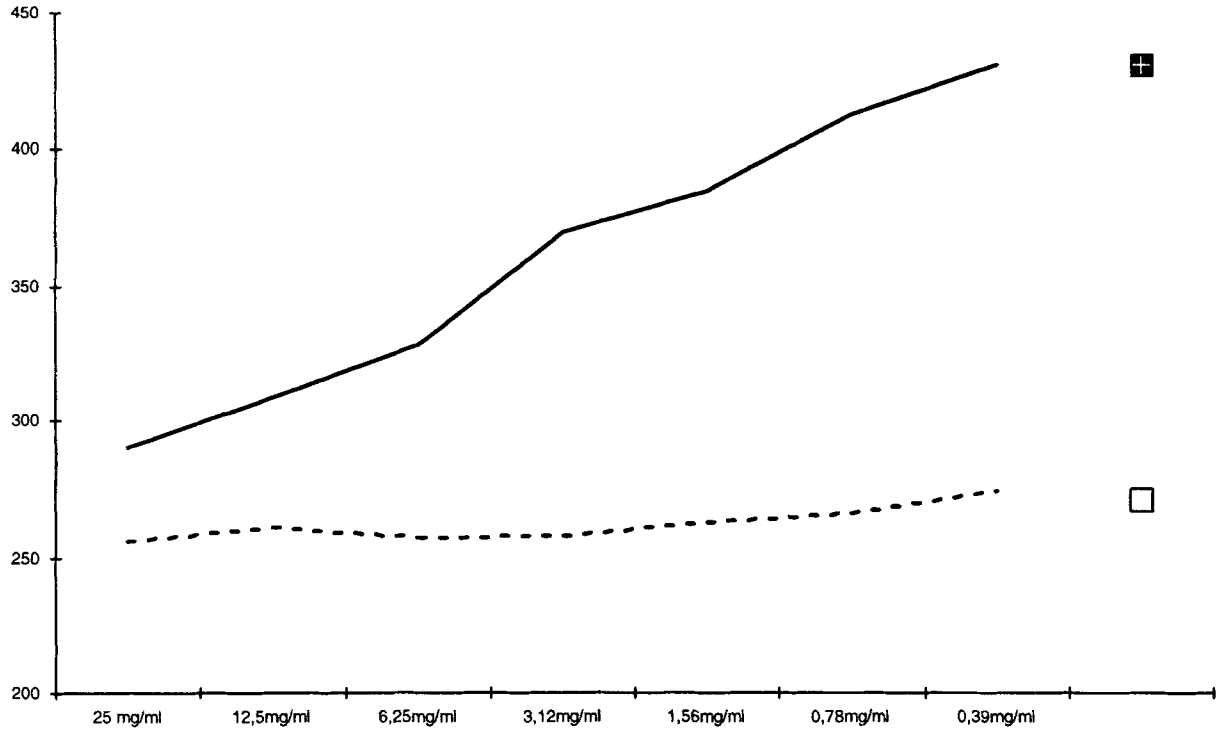


**Fig. 2** Inhibition of binding of a positive serum on a target cell by various dilutions of IVIgs. *Solid line* serum plus IVIgs, *dotted line* IVIgs alone, *open square* normal human serum, *solid square* positive serum alone

following weeks and months [36]. The titers are shown in Fig. 3. In more than half the patients, a significant and prolonged decrease was observed, with a stable titer 3 weeks after the last IVIg infusion. This decrease in cytotoxicity was paralleled by a decrease of binding to target cells in flow cytometry. Similar studies, performed on patients awaiting cardiac or renal transplants, yielded similar results [37, 38]. The decrease observed in antibody titer is long lasting and far exceeds the half-life of the infused IVIgs, suggesting a modification of the immune repertoire of the patients. We have demonstrated in some patients the appearance of anti-idiotypic antibodies; however, a more general modification of the B cell repertoire may be responsible, as seen with IVIg therapy after bone marrow grafting [39].

## IVIgs and transplantation

### Allowing transplantation through desensitisation

Following this first trial and the subsequent transplantation for some patients [40], we initiated another trial with the goal of transplantation for those patients with a

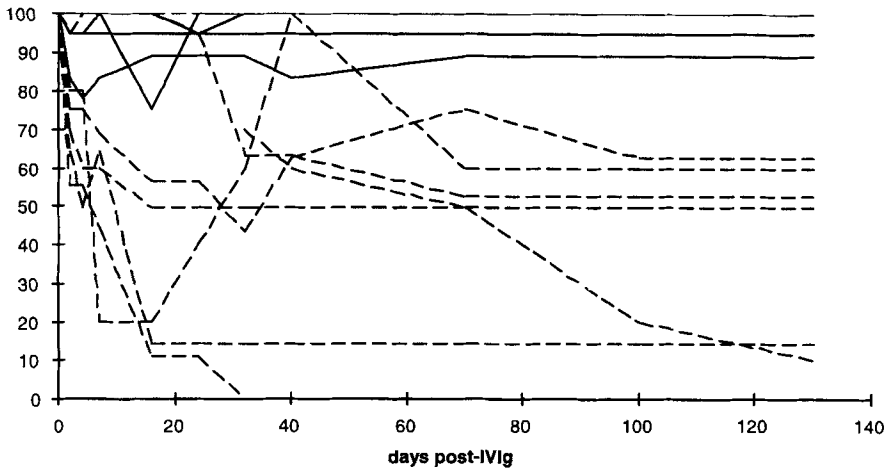


**Fig. 3** Evolution of the anti-HLA antibody titers after IVIg administration

decrease in antibody titres in the few weeks following desensitisation. A total of 15 patients have been treated, and 13 have received transplants [41, 42]. The patients had the following characteristics: mean age of 28 years and mean time on dialysis of more than 9 years; 13 had received previous renal transplants. Immunisation was due to transfusions and previous transplantation in 13 cases, a previous bone marrow transplant with multiple transfusions in one case, and multiples pregnancies with transfusions in the last case.

Eleven of the patients were given a cadaveric kidney after a mean decrease of 77% of their anti-HLA antibody titre, from 64% (86–42) to 15% (0–30). Two patients had a living, related donor, against whom the crossmatch was positive before IVIg treatment.

The immunosuppressive regimen associated IVIgs (1 g/kg at day 0 and day 1, and days 20 and 21, 42 and 43) with thymoglobulin (1 mg/kg per day) for 10 days, tacrolimus (from day 10 on), CellCept and steroids. One graft was lost to thrombosis a few hours post-transplantation, and one patient lost his graft due to rejection (with diffuse C4d staining). All other patients, including those with the living-related kidneys, have normal renal function and did not experience any episode of rejection after a mean follow-up of more than 18 months. At long-term follow-up, one graft had been lost to BK virus nephropathy, and two patients had died, one with previous leukaemia and bone marrow transplantation at 6 month post-transplantation, from PTLD, and one diabetic patient from stroke 1 year post-transplantation. Although no systematic biopsies were done, there is no evidence of accelerated chronic allograft nephropathy in the remaining patients. Similar results, using one to four administrations of 2 g/kg of IVIgs, have been reported by Jordan [43]. Very recently, the preliminary results of the first randomised, controlled study of the use of IVIgs to allow transplantation were presented by Jordan et al. [44]: 101 immunised patients (PRA $>50\%$) were allocated to receive either IVIgs (49 patients) or albumin (52 patients), at a dose of 2 g/kg body weight for four treatments. The level of anti-HLA antibodies, as determined by a classical cytotoxic PRA assay, was significantly decreased in the IVIg group, and, more importantly, 37% of the patients of the IVIg group underwent transplantation within a year, as compared to only 17% of the control group ($P<0.02$). Similar studies have been published in heart transplantation, with a decrease of 33% in the anti-HLA titers and a reduction of the waiting time [37].

Another technique uses repeated plasmapheresis coupled with low-dose (100 mg/kg) IVIgs, used here to prevent the rebound in antibody synthesis seen in earlier protocols. Montgomery et al. first reported the successful treatment of four patients [45], although all these patients experienced acute humoral rejection (AHR) post-transplantation, reversed by the same association of plasmapheresis and IVIgs. In follow-up reports of 33 patients by the same group, the rate of rejection fell to 64% [46, 47]. Gloor et al. added one dose of rituximab, as well as splenectomy, to the plasmapheresis/IVIg approach and could offer transplantation to 14 patients, with an overall rate of AHR (clinical or sub-clinical) of 43% [48, 49]. However, these patients had only an AHG-enhanced positive crossmatch against the donor, evoking the possibility that similar results could be attained with a less aggressive protocol. Heart transplantations have been performed against a positive crossmatch pre-IVIg, with good results, under a treatment of both plasmapheresis and IVIgs [38, 50]. This is most important in the case of patients receiving circulatory assistance, where sensitisation results from multiple exposures to blood products [51].

## IVIgs at the time of transplantation for prevention of acute rejection

IVIgs have been used for prophylaxis of acute rejection in patients deemed at high risk for rejection, such as hyperimmunised patients, second transplants, and children receiving kidney and cardiac transplants. Besides their effects on anti-HLA antibodies, other mechanisms of action could be at play, including the inhibition of lymphocyte proliferation in response to alloantigens [22], modulation of CD8 positive T cell function [25] or potentiation of cyclosporin A efficacy [52].

A retrospective study was performed on 21 immunised patients receiving their first transplant [53]. Those patients received IVIgs (0.4 g/kg per day from day 0 to day 5) in addition to a quadruple sequential immunosuppressive regimen consisting of anti-lymphocyte antibodies, azathioprine, steroids and delayed cyclosporin A. Graft survival at 2 years was 95%, well above published results for this type of patient (approximately 80%). A paediatric study on 52 children demonstrated a better graft survival at 1, 2 and 3 years (95%, 95% and 88% versus 88%, 79% and 79%) in children at high risk for cytomegalovirus (CMV) infection treated with IVIgs, than a control, low risk group without IVIg therapy. Interestingly, there were no differences in CMV infection between the two groups [54]. Last, a randomised study using IVIgs as prophylaxis for acute rejection was performed on 41 patients receiving their second graft [55]. Twenty-one patients received 0.4 g/kg per day from day 0 to day 5, with a classical sequential quadruple immunosuppressive regimen. Five-year graft survival was significantly higher in the IVIg-treated group (68%, versus 50% in the control group). A similar study in heart transplantation demonstrated that the survival of 16 immunised patients treated with IVIgs and plasmapheresis was identical to the survival of non-immunised patients [56].

IVIgs as a treatment for rejection

IVIgs are sometimes used to treat established rejection, most notably in patients with poor health status, to avoid the consequences of anti-lymphocyte antibody therapy [44, 57]. In most cases, the rejection was steroid-resistant and often with ominous vascular lesions. IVIgs could act in those cases, either by neutralisation of circulating anti-endothelial antibodies, as demonstrated in xenotransplantation [58, 59, 60], or by blocking endothelial cell activation, an essential step in the genesis of the vascular lesions [24]. In a prospective randomised study of 30 steroid-resistant rejections, Casadei et al. showed that IVIgs had the same efficacy as OKT3, rescuing 73% of the grafts without the well-known side effects of OKT3 [61]. The combination of IVIgs and plasmapheresis has also been used in this setting, first by the Johns Hopkins group [45], with remarkable results, and confirmed by Rocha et al. in a retrospective study of 16 acute humoral rejections with an 81% graft survival rate at 1 year post-rejection [62].

## Conclusion

In conclusion, the administration of IVIgs is now part of the therapeutic approach commonly used in allotransplantation, with three major indications. IVIgs are used alone or in combination with plasmapheresis to allow transplantation in immunised patients; the use of these therapies in the prophylaxis and treatment of rejection needs further study.

Finally, the use of IVIgs, together with the more sophisticated techniques now used for the detection of anti-HLA antibodies, clearly calls for a re-appraisal of the contra-indication for transplantation in the case of anti-donor antibodies.

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