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Anti-HLA antibody repertoire after IVIg infusion in highly sensitised patients waiting for kidney transplantation

A Geneva-Lausanne Pilot Study

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Summary

Polyclonal intravenous immunoglobulin (IVIg) treatment reduces crossmatch positivity and increases rates of transplantation in highly sensitised patients (HS). We quantified the panel reactive antibody (PRA) by microlymphocytotoxicity (MLCC), and we analysed anti-HLA class I and class II IgG specific antibody repertoire by Luminex before and after IVIg infusion alone in HS patients awaiting kidney transplantation.

Five patients received three monthly infusions of 1 g/kg of IVIg. Serum samples collected pre and post IVIg treatment were submitted for PRA analysis by MLCC. Anti-class I and anti-class II antibody specificities were then tested by Luminex. We focused on the anti-HLA class I and class II antibodies directed against HLA expressed by a previous graft. We also analysed the anti-HLA antibody repertoire in three patients who had not received IVIg infusion. The PRA level determined by MLCC decreased significantly in one of the five patients, dropping from 40% to 17%. The Luminex assay showed fluctuations of the anti-HLA antibody levels over time, but no significant long-term modifications of the anti-HLA antibody repertoire were observed, even in the patient with a strong and prolonged reduction of the PRA determined by MLCC.

Our results show that IVIg at 1 g/kg is not sufficient to reduce PRA and does not modify the repertoire of specific anti-HLA antibody determined by Luminex.

Keywords: anti-HLA antibody; IVIg; kidney transplantation

Introduction

The presence of antibodies against donor HLA is associated with hyperacute or severe acute rejection, often leading to graft loss [1, 2]. HLA anti-donor antibodies are detected by a crossmatch testing. If positive, the result is a contra-indication for kidney transplantation. In Switzerland, 10% of patients on a waiting list for a first kidney transplant are immunised with anti-HLA antibodies. This number rises to 55% for those waiting for a re-transplantation [3]. Immunisation can occur after blood transfusion [4], pregnancy [5] or any organ transplantation [1, 2, 6]. Different approaches have been used to try to decrease HLA antibodies in hyperimmunised patients. Desensitisation with plasmapheresis or immunoabsorption may help remove anti-HLA antibodies but these methods are associated with a rapid re-emergence of anti-HLA antibodies [7–9]. Several teams have successfully decreased anti-HLA antibody levels in highly immunised (HS) patients awaiting kidney or heart transplantation, using polyclonal intravenous immunoglobulins (IVIg) [10–15]. The efficacy of the therapy has been attributed to several mechanisms including the presence of IgG anti-idiotype antibodies, saturation of Fc receptors on the macrophage surface, inhibition of complement-mediated injury, inhibition of inflammatory cytokine production, inhibition of T and B lymphocyte proliferation, and antibody production [16–24]. A dose of 2 g/kg of IVIg was used in

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the most recent studies [12, 13, 25], but doses of 0.4 g/kg or 0.1 g/kg in addition to plasmapheresis have also been shown to reduce the PRA MLCC, or to induce negative crossmatch [11, 25]. The inhibitory effet of the IVIg on HLA-alloantibody has been tested *in vitro* by several groups with controversial results depending on the readout used in the study [14]. However, nothing is known on the *in vivo* effect of IVIg given without additional immunosupressive drugs on HLA-alloantibody repertoire determined by high sensitive technology recently developed.

In this study, using Luminex we analysed the impact of IVIg given alone on the anti-HLA antibody repertoire in a group of patients who received IVIg infusions at an intermediate dose of 1 g/kg.

Material and method

Patients

The study included five HS patients with anti-HLA alloantibodies (isotype IgG) due to a blood transfusion, pregnancy or prior organ transplantation, and who had been waiting for a cadaveric donor kidney transplantation for at least one year. Only those patients with a PRA that had remained stable (less than 20% fluctuation) for at least one year were eligible for the study. Patients received at least three monthly infusions of 1 g/kg of IVIg Redimmune® (ZLB Behring AG) in addition to their usual treatment. None of them were transfused during the time of the study and none of them were given immunosuppressive drugs. Serum samples were analysed before, as well as 1 month and 6 months after the last IVIg infusion. Because he was successfully desensitised, patient 4 received three additional IVIg infusions and late time points were analysed**.** Three additional HS patients who did not receive IVIg infusions but who had been on the waiting list for several years were also analysed. Serum samples from these patients were assessed over a period of at least six months. None of them received blood transfusions during the study. None of them were on immunosuppressive drugs. The study was approved by the ethics committee of the institution and all patients had signed an informed consent.

Panel Reactive Antibody (PRA)

To quantify the panel-reactive antibody in study patients, serum samples were tested in a microlymphocytotoxicity assay (MLCC) against an HLA-typed lymphocyte panel of *30 cells*. Lymphocytes were isolated by Ficoll, washed, and dispensed into oiled Terasaki trays containing 1 µl of patient tested serum per well. Cells were incubated with serum for 30 min at 21°C and then with complement for 3 h (PBL) or 2 h for T cells isolated on Dynabeads (HLA Cell Prep 1; Dynal, Great Neck, NY) [26].

Luminex technology

LABScreen® class I and class II uses a panel of HLA-antigens coated on the surface of colour-coded microspheres to determine percent PRA and to identify antibody specificities. Serum samples were collected from the patients and stored at –20 °C until use. 5 µl of class I panel (LS1PRA, LABScreen® PRA and LS1A01, LABScreen® Single Antigen) or class II panel (LS2PRA, LABScreen® PRA and LS2A01, LABScreen® Single Antigen) microbeads (Luminex Corporation, Austin, Tx) were added to 20 µl of serum, and the mix was incubated for 30 min at room temperature and processed according to manufacture instructions (One Lambda, Inc) [27]. Anti-HLA antibody detection and results interpretation were performed using LABScan™ 100 software (One Lambda, Inc.) on the Luminex® 100™ instrument (Luminex Corporation). Serum samples of each patient were analysed with the same batch of LABScreen® Class I and II. The intensity of anti-HLA antibody is scaled 2, 4, 6, or 8 by Luminex. 2 is negative, 4 is intermediate, 6 and 8 are clearly positive.

Results

Study characteristics and adverse events

The characteristic of the five patients included in the study, their diagnosis and the number of transplantations before being included in the study are described in table I. PRA values were those recorded at the time of entry in the study. To compare the effect of IVIg with the natural fluctuations of anti-HLA antibodies, three additional stable patients were also extensively analysed. The characteristics of the patients who did not receive IVIg are also described in table 1. PRA values ranged from 39 to 100% in patients treated and non-treated before the beginning of the IVIg treatment (table 1). The infusions were performed during an off-dialysis day. Infusion symptoms, including headaches, were monitored during, at the end, and 1 h after infusion. Only one patient described mild episodes of headaches during two infusions. Therefore, in this study, infusion of IVIg at 1 g/kg is considered to be safe.

Panel Reactive Antibody determined by microlymphocytotoxicity (PRA MLCC) before and after IVIg

PRA levels were first determined by MLCC at specified intervals during the study period and one month after the last IVIg infusion. Because the PRA MLCC is not specific for anti-HLA antibody, the serum samples of all patients were tested and found positive with a specific anti-IgG HLA antibody Elisa assay. Lambda Antigen Trays (LAT™, One Lambda Inc., Canoga Park, CA), which feature purified HLA Class I and Class II antigens attached to a Terasaki-format tray, are designed for the detection of HLA IgG antibody (data not shown). The fluctuations of the PRA MLCC in the control group are shown in figure 1B.

Because patient 4's PRA fell by more than 50% the patient received three additional monthly IVIg infusions (figure 1C, arrows), and the PRA MLCC remained at low levels after the three additional in-

Table 1

Clinical characteristics of patients included in the study.

Patient[a]	Age (years)	Gender[b]	Prior grafts	Diagnosis[c]	PRA % by MLCC[d]	Nb of MM[e] (total)
P1	58	F	1	SLE	72%	2
P2	38	M	2	GN	39%	9
P3	59	M	1	GN	61%	2
P4	39	M	1	Reflux	45%	4
P5	62	F	3	SLE	50%	10
C6	43	F	2	IDD	100%	6
C7	69	F	1	GN	68%	3
C8	54	F	0	PKD	61%	–

[a] P1 to P5 refer to patients 1 to 5, receiving IVIg treatment as described in Material and Method. C6 to C8 refer to control patients 6–8, not receiving IVIg.
[b] F, female; M, male
[c] SLE = systemic lupus erythematous (non active), GN = glomerulonephritis IDD = insulin-dependent diabetes, PKD = polycystic kidney disease
[d] PRA, panel reactive antibodies detected by microlymphocytotoxicity (MLCC) on 30 cells at the beginning of the study
[e] Nb of MM, number of mismatch A B DR between the patient and previous transplant(s)

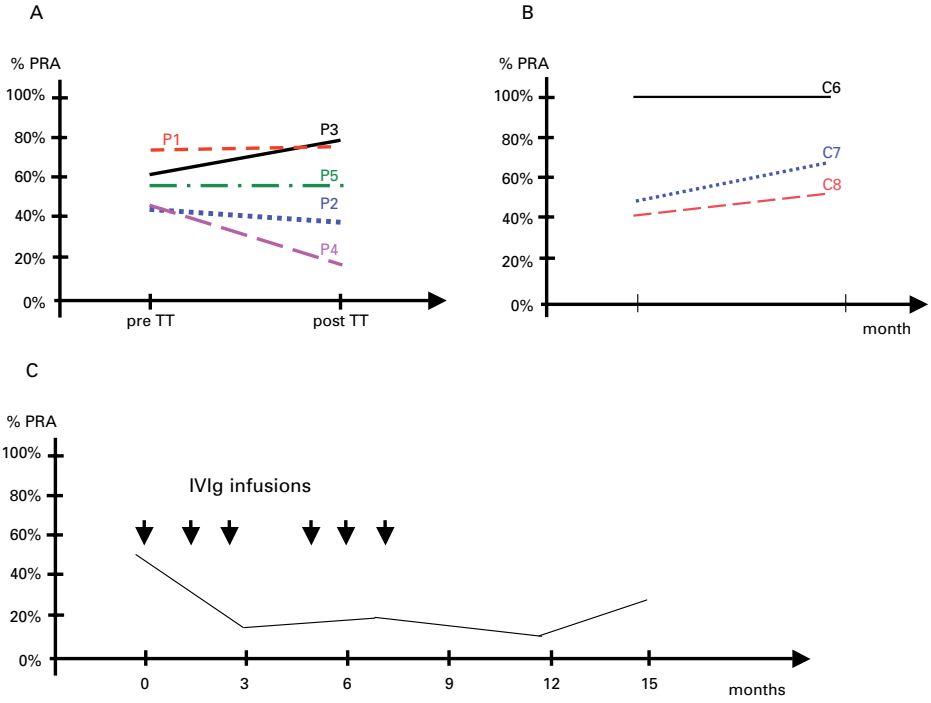


Figure 1

Changes in Panel Reactive Antibody determined by microlymphocytotoxicity (PRA MLCC) during the study.
A Changes in PRA levels before and after three monthly infusions of IVIg 1 g/kg in sensitised patients awaiting kidney transplantation (P1 to P5)
B Changes in PRA levels over a 6-month period in sensitised patient awaiting kidney transplantation, not receiving IVIg (C6 to C8)
C Long-term changes in PRA levels in patient 4. Patient 4 received three monthly infusions of IVIg before decreasing his PRA, and a further three monthly IVIg infusions. The IVIg infusions are indicated as arrows.

fusions. However, a slow but constant increase of PRA MLCC was recorded in the weeks following the last IVIg infusion, which showed that the reduction of PRA MLCC was only temporary (figure 1C).

Analysis of anti-HLA antibody specificity by Luminex before and after IVIg

Every patient included in the study (except control patient 8) had had one or more previous transplantations. Consequently, we analysed more precisely the specificities of HLA class I and class II antibodies of each patients, focusing on the HLA antigens expressed by previous grafts before IVIg treatment, at the end of the monthly treatment and a few months after the last IVIg infusion (figure 2). Each anti-HLA specific antibody in figure 2 was detected by LABScreen® PRA and confirmed by LABScreen® Single Antigen. For HLA class I, fluctuations of the specific anti-HLA antibodies after the three IVIg infusions were observed in all patients (figure 2A left). The fluctuations were transient in patients 1 and 2. In patients 3 and 5, we observed a small but persistent decrease in the intensity of all specific anti-HLA class I antibodies. In patient 4, a sustained increase of the specific anti-HLA class I antibodies intensity was recorded. These results contrast with the persistent drop of PRA MLCC shown in figure 1. For anti-HLA class II antibodies (figure 2A right), we observed a transient reduction of specific anti-HLA antibodies in patients 1 and 5, and an increase of specific anti-HLA antibodies in patients 2 and 4. Patient 3 had a persistent absence of anti-HLA

Figure 2

Changes in Donor Specific Antibodies (DSA) during the study determined by Luminex.

A For each patient, we focused our analysis on anti-HLA antibodies developed against HLA antigens of a previous graft determined by LABScreen® PRA Class I (left column) and LABScreen® PRA Class II (right column). The anti-HLA antibodies detected were confirmed by LABScreen® Single Antigen (data not shown). The levels of anti-HLA antibodies with intensities of 6 and 8 are calculated as the ratio between the mean fluorescence of each serum-HLA microbead and the mean fluorescence of the positive control (LABScreen® PRA). Due to the high sensitivity of this test, only intensities of 6 *and* 8 were taken into account.
Anti-HLA antibodies were analysed before IVIg infusion at the end of the treatment (End TT) and 6 months after (distant). We also report the result of patient 4 after the first (End 1st TT) and second (End 2nd TT) IVIg infusion.

B In control patients, we analysed anti-HLA antibodies developed against HLA antigens of a previous graft over time (3 and 6 months). Anti-HLA antibodies developed against HLA antigens of a previous graft determined by LABScreen® PRA Class I (left column) and LABScreen® PRA Class II (right column). The anti-HLA antibodies detected were confirmed by LABScreen® Single Antigen (data not shown). As control patient 8 had not received a prior graft, we analyzed the major anti-HLA antibodies detected. Due to the high sensitivity of this test, only intensities of 6 and 8 were taken into account.
TT = treatment

Figure 2a

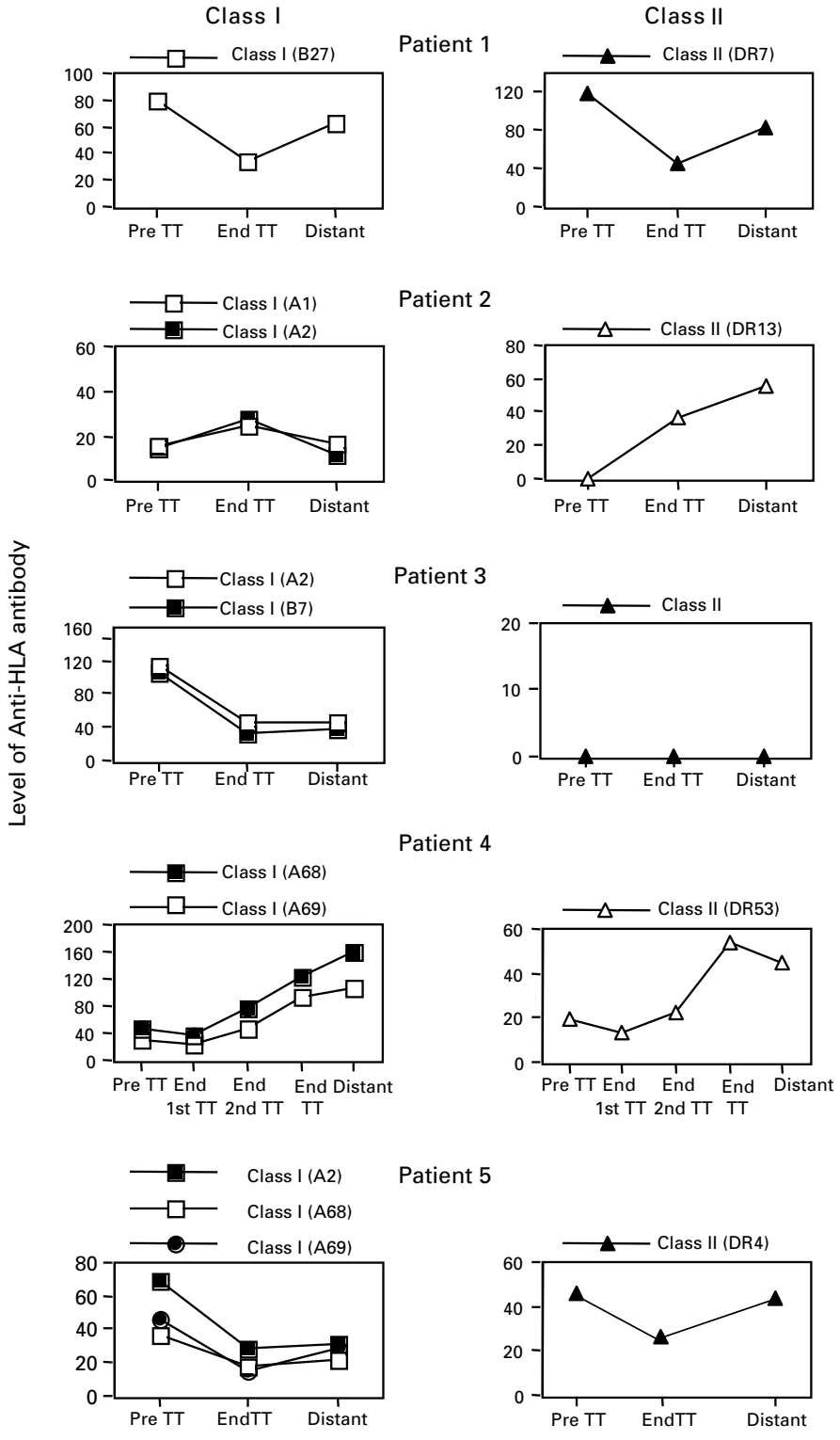
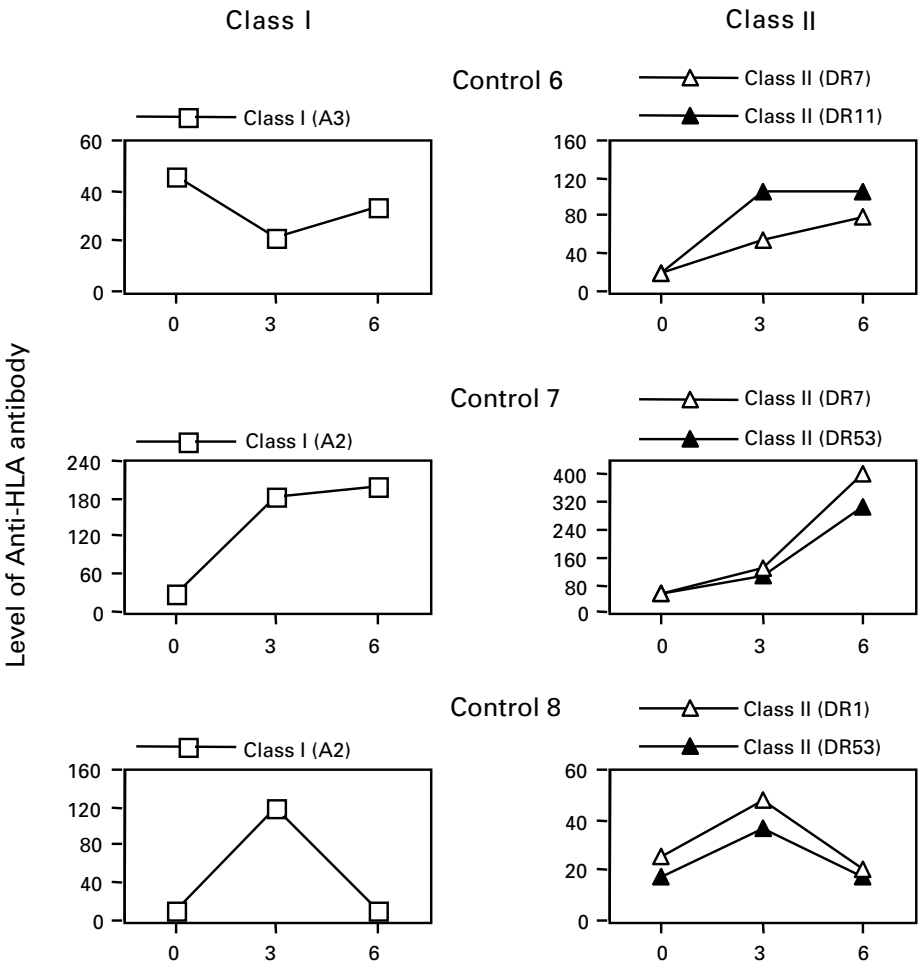


Figure 2b



class II antibody (figure 2A right). To compare our results with the control group, we assessed the anti-HLA specific antibodies over time in the 3 HS patients (table 1) who did not receive IVIg treatment. In this group, we observed comparable fluctuations of the anti-HLA antibodies intensity for both HLA class I and class II specific antibodies (figure 2B).

Discussion

Our study showed that IVIg infusion at the dosage of 1 g/kg was safe but induced a significant reduction of the PRA MLCC in only one of our five patients. Anti-HLA antibody levels, measured with a highly sensitive technology, fluctuate naturally over time, with or without IVIg treatment. Therefore our data suggested that IVIg alone had no direct effect on specific anti-HLA antibody repertoire.

These results in a small group of HS patients are much less impressive than those reported in previous studies, where a greater number of patients obtained a significant reduction of the PRA [11–14] with IVIg at 2 g/kg [12, 13, 25], at 0.4 g/kg or 0.1 g/kg in addition to plasmapheresis [11, 25, 28]. Although IVIg is generally used at 2 g/kg to treat several autoimmune diseases, very few studies have been designed to compare IVIg dosages in these disorders. Besides, IVIg at 1 g/kg has been shown to be effective in ITP [29] and myasthenia gravis [30]. Due to the price of IVIg treatment and its side effects, some of which have been shown to be dose related, it made sense to try to find the most cost effective IVIg dosage for such therapy. Our results suggested that 1 g/kg was not sufficient to reduce the PRA MLCC in a significant number of patients. The discrepancy in the results obtained by other investigators can be due to the difference in dosage and numbers of cure. However, it is difficult to compare these studies because some groups infused IVIg in addition to plasmapheresis or other immunosuppressive drugs and determined the effect by crossmatch with potential donors [25]. Crossmatching remains the final test before kidney transplantation, but as it is not highly sensitive and dependent on anti-HLA cytotoxic antibody, it is of great interest to identify precisely the anti-HLA antibody repertoire with a highly sensitive approach to decrease the risk of humoral rejection after transplantation. The

highly specific and sensitive Luminex technology is considered as an accurate approach for the detection of anti-HLA antibodies [31]. We used this technology to determine the repertoire of anti-HLA antibodies in HS patients waiting for kidney transplantation. The absence of any reduction in PRA MLCC after IVIg infusion does not mean that specific anti-HLA antibodies could not be targeted by the IVIg treatment. Our data show that the anti-HLA antibody repertoire analysed by Luminex did not demonstrate any prolonged difference before and after IVIg treatment. Surprisingly the HLA antibody repertoire in patient 4 whose PRA levels determined by MLCC dropped significantly were not modified either. We can argue the dose of IVIg were not sufficient to reduce the anti-HLA antibodies detected at high level (intensity of 6 and 8). However, when we checked anti-HLA antibodies present at a lower level (intensity of 4), we did not observe any significant modification of the anti-HLA repertoire after IVIg treatment either (data not shown). Wassmuth et al. strongly suggest that the inhibitory effet of the IVIg on HLA-alloantibody tested *in vitro* is related to interaction with complement rather than anti-idiotypic antibodies [32]. Our *in vivo* data tend to confirm the *in vitro* results found in this study [32]. The persistence of a high level of anti-HLA antibodies after IVIg treatment without modification of the repertoire is a strong argument against a direct inhibition of the specific antibody production by B cells and plasma cells, or the presence of anti-idiotypic antibody able to block anti-HLA antibodies.

A far as we know, the impact of anti-idiotypic antibodies at the level of anti-HLA antibodies has never been demonstrated. Commercially available IVIg has been shown to contain anti-idiotypic antibodies able to neutralise autoantibodies in selected autoantibody-mediated autoimmune diseases [33–36], and to down-regulate the synthesis of antibodies by B cells that express the relevant idiotype [18]. However, a recent report demonstrated that IVIg preparations from multiparous women have increased levels of anti-idiotypic antibodies specific for anti-HLA alloantibodies which can significantly inhibit an established IgG anti-HLA immune response in a humanised SCID mouse model [37].

Our data suggest that at this dosage, IVIg alone may not be sufficient to eliminate specific alloantibodies in HS patients. It might necessitate an association with other immunosuppressive drugs, as demonstrated by Zachary et al. who combined low-dose IVIg (CMV-Ig), plasmapheresis and quadruple sequential immunosuppression [25], or an association with monoclonal antibody such as anti-CD20 to achieve this objective [38, 39].

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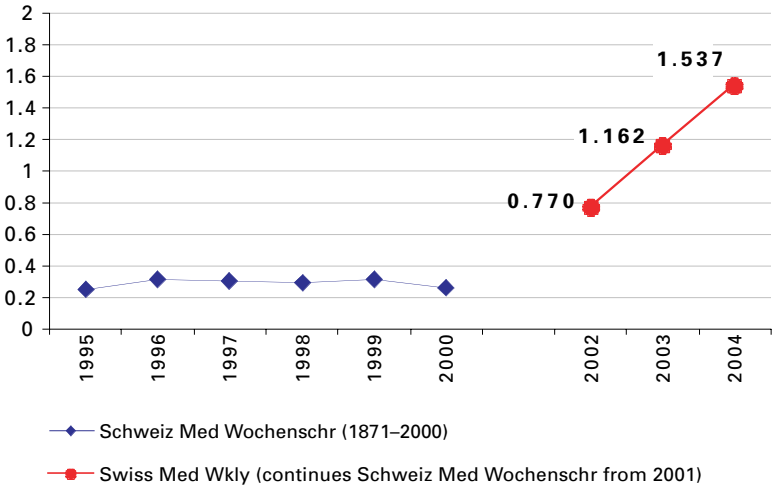

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