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Pregnancy and donor-specific HLA-antibody-mediated rejection after liver transplantation: “Liaisons dangereuses”?

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ABSTRACT

Background: Risk factors for the development of anti-HLA antibodies include blood transfusion, organ transplantation, and pregnancy. Humoral rejection, mediated by donor-specific anti-HLA antibodies (DSA), has been studied in all kind of solid organ transplantations, and several studies have suggested that post-liver transplantation (LT) DSA may play a role in acute and chronic rejection.
Objective: The aim of the present study was to assess the impact of pregnancy on the occurrence of DSA and the impact of DSA in a large population of young female LT recipients.
Methods: This single center retrospective study included all female patients who underwent a first LT between January 1990 and December 2010 and who were of childbearing age during post-LT follow-up (*i.e.* 18 to 40 years old).
Results: The study population consisted in 73 patients, and the mean age at LT was 20.9 years (0.6–39.9); 32 patients were transplanted during childhood. The global incidence of *de novo* DSA was 42.5% (31/73), after a median delay of 15.5 years (1–25) of follow-up after LT. Most *de novo* DSA were anti-class II alone (90.3%), and included anti-DQ for 80.6%. From the 73 patients, 33 presented at least one pregnancy after LT (45.2%) and before DSA screening. Multivariate analysis disclosed that history of pregnancy (OR = 6.37; 95%CI, 2.17–18.63, p = 0.001) and younger age at LT (OR = 0.96; 95%CI:0.92–0.99, p = 0.033) were significantly associated with *de novo* DSA. Among the 31 patients who had *de novo* DSA, the diagnosis of antibody-mediated rejection was made in 8 patients (25.8%), after a median delay of 74 months after LT; 6/8 (75.0%) had history of pregnancy. During follow-up, 3 of these 8 patients lost their liver graft and died.
Conclusion: The results of the present study suggest that close monitoring of DSA in young women with history of pregnancy should be recommended regarding the risk of DSA-mediated rejection.

1. Introduction

Antibodies-mediated rejection (AMR) is related to donor-specific anti-HLA antibodies (DSA) and has been extensively studied in all kind of solid organ transplantations including recently liver transplantation (LT) [1]. Outside the field of LT, many studies have shown that both preformed and *de novo* DSA were associated with increased risk of acute rejection and graft failure [2–5]. Nevertheless, it has been suggested since the early 90's that positive crossmatch could increase risk of early graft loss after LT [6–9]. Similarly, in the more recent years, several studies have shown that post-LT DSA may play a role in acute and chronic rejection [10–13].

Risk factors for the development of anti-HLA antibodies include history of blood transfusion, organ transplantation (modulated by post-transplantation immunosuppression), and pregnancy. Huyn et al. evaluated how different sensitization events affect the panel-reactive

Abbreviations: LT, liver transplantation; DSA, donor specific antibody; HLA, Human leukocyte antigen; CNI, calcineurin-inhibitors; CsA, cyclosporine; Tac, tacrolimus; MMF, mycophenolate mofetil

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antibody status in 674 (354 males and 320 females) solid organ transplant candidates [14]. Reactive antibody (class I and/or II)-positive rates were significantly higher in patients with transfusion (33.0%), pregnancy (71.4%), or transplantation events (76.9%) than in patients without any sensitization events (5.6%). Transplantation had the strongest immunization effect, especially for class II HLA antigens. Female compared with male patients (60.3% *vs.* 34.2%) and re-transplantation, compared with first transplantation candidates of kidney transplantation (80.2% *vs.* 41.1%) showed significantly higher rates. The aim of the present study was to assess the impact of pregnancy on the occurrence of *de novo* DSA and the impact of these DSA on graft outcome in a large population of young female LT recipients.

2. Patients and methods

2.1. Study design

The present single center retrospective study included all female patients who underwent a first LT between January 1990 and December 2010 at the Edouard Herriot University Hospital (Lyon, France) who were of childbearing age during post-LT follow-up (*i.e.* 18 to 40 years old) and who had both at least one screening for anti-HLA antibodies at day of transplantation (Day 0) and another screening after LT. Pre- and post-LT pregnancies and transfusions were recorded for all patients.

All transplantations were ABOc LT. The initial immunosuppressive regimen was based on calcineurin inhibitors: ciclosporine or tacrolimus. In addition, patients received 500 mg of methylprednisolone after reperfusion. Induction with polyclonal or monoclonal antibodies was performed in some recipients and in cases of renal failure at the time of the LT for delayed CNI introduction. On postoperative day 1, we began tapering methylprednisolone which was maintained at 20 mg/day thereafter, then tapered to a maintenance dose of 0 to 5 mg/day after 12 months post-transplantation. Azathioprine, mycophenolate mofetil, or everolimus (EVR) were either administrated as a part of initial triple immunosuppressive regimen, or introduced during follow-up as maintenance immunosuppressive agents.

Screening was performed retrospectively on historical serum samples for the anti-HLA antibodies before 2010, and prospectively after 2010. DSA were considered as *de novo* when not present at D0. Timing between LT and DSA screening was calculated as the interval between transplantation, and either the last negative DSA screening or the first positive DSA screening. Concerning DSA screening from historical serum, it was usually performed at 1-, 5- and 10-years protocolized evaluation after transplantation (serum were obtaines from our virology department).

Liver function tests (serum aspartate aminotransferase – AST, alanine aminotransferase – ALT, gamma-glutamyl transpeptidase – GGT, alkaline phosphatase – ALP, total bilirubin – TBil, direct bilirubin – DBil, and indirect bilirubin – IBil) and measurement of immunosuppressive drug blood levels were performed by the hospital's laboratory during hospitalizations, and externally before routine patient visits.

Protocol liver biopsies were planned at 1, 5 and every 5 years thereafter from transplantation. All biopsies performed for liver function test abnormalities and protocol biopsies were reviewed. For diagnosis and grading of allograft rejection, Banff classification published in 1997 and updated in 2000 (19) was used. All liver biopsies with features of rejection were reviewed and the histological diagnosis of AMR, including C4d staining, was made from the Banff update of 2016 (23).

To identify risk factors for *de novo* DSA and their impact, the DSA-positive and DSA-negative populations were compared with regards to clinical data.

2.2. Immunological analyses

All analyses were performed in a blinded fashion by a trained immunobiologist (V.D. at the Etablissement Français du Sang, Lyon, France). HLA typing of donors and recipients was performed by Luminex PCR-SSO reverse (One Lambda, Canoga Park, CA, US). Serum samples were analyzed using Luminex Single Antigen Flow Beads assays (LSA class I and class II, Lifecodes, Immucor, Norcross, GA, US). The mean fluorescence intensity (MFI) was measured on a LABscan IS 200, and all the specificities were evaluated with the company's defined threshold such as MFI $\geq$ 1500 and AD-BCR $\geq$ 5 to define positivity (AD-BCR is a ratio of adjusted MFI to the quantity of coated antigen per bead). The positivity of these two criteria together allows us to consider the corresponding specificities as a preformed DSA. In some few cases, only the AD-BCR is higher than 5, with MFI between 500 and 1500. In these cases, the DSA is validated only for post transplantation follow-up (*de novo* DSA) when the corresponding graft mismatch Antigen is not included in a CREg positive reaction.

2.3. Statistical analysis

Categorical variables were expressed as percentages and compared with the Chi-squared or Fischer's exact-tests. Continuous variables were expressed as mean $\pm$ SD and compared using the Student's *t*-test or the Mann-Whitney's test in case of non-Gaussian distributions. Patient survival was calculated from the date of LT to that of death or the final clinical visit. Graft survival was calculated from the date of LT to that of retransplantation, death or last visit if there was no retransplantation. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. The predictive factors for developing *de novo* DSA were determined by univariate and multivariate regression analyses. A p value $< .05$ was considered statistically significant. Statistical analyses were performed using SPSS software, version 13.0 (IBM, Armonk, NY, US).

3. Results

3.1. Study population

During the 1990–2016 periode, a total of 101 female LT recipients of childbearing age were followed in our center. Among these, 73 were screened for anti-HLA antibodies on the day of transplantation, and also had at least one other screening after LT and were included in the study population. The mean age at LT was 20.9 years (0.6–39.9); 32 patients were transplanted during childhood. After LT, 33 patients experience one or more pregnancies (including miscarriages or interrupted pregnancies). Immunosuppressive regimen at the time of pregnancies consisted in tacrolimus (n = 27, 81.8%), cyclosporine (n = 6, 18.2%), MMF (n = 6, 18.2%), azathioprin (n = 3, 9.1%), corticosteroids (n = 7, 21.2%). For patients under MMF, pregnancies were unexpected.

From the study population, 3 patients (4.1%) had preformed DSA (all had history of pregnancy before LT), and 31 patients (42.5%) developed *de novo* DSA, after a median delay of 15.5 years (1–25) of follow-up after LT. Most *de novo* DSA were anti-class II alone (90.3%), and included anti-DQ for 80.6%. Median maximal MFI was 7500 (600–17,500) for *de novo* DSA.

3.2. Risk factors for DSA

Post-LT presence of *de novo* DSA was significantly more frequent in patients with history of pregnancy and in pediatric LT recipients (Table 1). Recipient age, at the time of LT was also significantly lower in patients who developed *de novo* DSA. Living donor LT (*vs.* cadaveric), history of massive red blood cells transfusion, history of platelets transfusion, initial immunosuppressive therapy, maintenance immunosuppressive therapy or trough level of tacrolimus were not associated with the presence of *de novo* DSA. Multivariate analysis disclosed that history of pregnancy (OR = 6.37; 95%CI, 2.17-18.63, p = 0.001) and younger age at LT (OR = 0.96; 95%CI:0.92-0.99, p = 0.033) were significantly associated with *de novo* DSA.

Table 1
Risk factors for *de novo* DSA.

	de novo DSA (n = 31)	No *de novo* DSA (n = 42)	p-Value
Age at LT (years), mean ± SD	15.8 ± 12.1	24.4 ± 14.1	0.0077
Pediatric LT (*vs.* adult), n (%)	19 (61.3)	15 (35.7)	0.019
Living donor (*vs.* cadaveric), n (%)	5 (16.1)	10 (23.8)	0.610
Initial immunosuppressive therapy, n (%)			
Tacrolimus (*vs.* cyclosporine)	17 (54.8)	28 (66.7)	0.286
Mycophenolate mofetil (*vs.* azathioprine or none)	14 (45.2)	26 (61.9)	0.236
Steroids (first year)	20 (64.5)	30 (71.4)	0.708
Maintenance immunosuppressive therapy*, n (%)			
Tacrolimus (*vs.* cyclosporine)	26 (83.9)	33 (78.6)	0.727
Mycophenolate mofetil (*vs.* azathioprine or none)	16 (51.6)	23 (54.8)	0.790
Steroids	7 (22.6)	7 (16.7)	0.526
Trough level of tacrolimus*, mean ± SD	3.9 ± 2.1	4.2 ± 1.9	0.28
Pregnancy after LT, n (%)	22 (71.0)	11 (26.2)	< 0.0005
History of massive (> 10) red blood cells transfusion, n (%)	13 (41.9)	22 (53.4)	0.517
History of platelets transfusion, n (%)	10 (32.3)	19 (45.2)	0.380

* At the time of DSA screening.

3.3. AMRs

Among the 31 patients who had *de novo* DSA, the diagnosis of antibody-mediated rejection was made in 8 patients (23.6%), after a median delay of 74 months after LT; 6/8 (75.0%) had history of post-LT pregnancy. These patients had class II DSA, with MFI ranging from 1500 to 28,600, and liver graft dysfunction. In 4 patients, treatment consisted of steroids, rituximab, plasmapheresis, and immunoglobulins. During follow-up, 3 of these 8 patients lost their grafts and died.

3.4. Survival

According to Kaplan-Meier estimates, patient and graft survivals were not significantly different according to the presence or not of *de novo* DSA (Fig. 1A and B).

In the group of patients without DSA, causes of death/graft loss were chronic rejection (n = 3), ischemic cholangiopathy (n = 1), or recurrent initial disease (n = 1). In the group of patients with DSA, causes of death/graft loss were chronic rejection (n = 4), recurrent initial disease (n = 2), or lung carcinoma (n = 1).

4. Discussion

We report herein that post-LT pregnancy is associated with an increased risk for the development of *de novo* DSA, and thereafter DSA-mediated rejection, with poor outcome in some cases. The impact of DSA on patient and graft survival after LT has been more extensively studied in the recent years, and it has been suggested that presence of DSA could be associated with higher risk of rejection and decreased liver allograft survival after adult or pediatric LT in most [8,9,13,15–23], but not all studies [24–27]. In our present study, there was a numerical difference in patient death and/or graft loss according to the presence or not of DSA, and the lack of statistical significance was probably related to the small number of patients. Results and interpretation may depend on DSA type (preformed or *de novo*), DSA class (I or II) and cut-off value with Luminex assays, together with the period of follow-up after LT (1-, 5-, 10-, 15-, 20-years). In the large study of Kaneku et al., 8.1% of LT recipients developed *de novo* DSA with a MFI > 5000 1-year after transplantation, and almost all *de novo* DSA were against HLA class II antigens (the majority against DQ antigens). This strongly recalls our present results. In addition, multivariable analysis disclosed that the use of cyclosporine (as opposed to tacrolimus) and low calcineurin inhibitor levels increased the risk of *de novo*

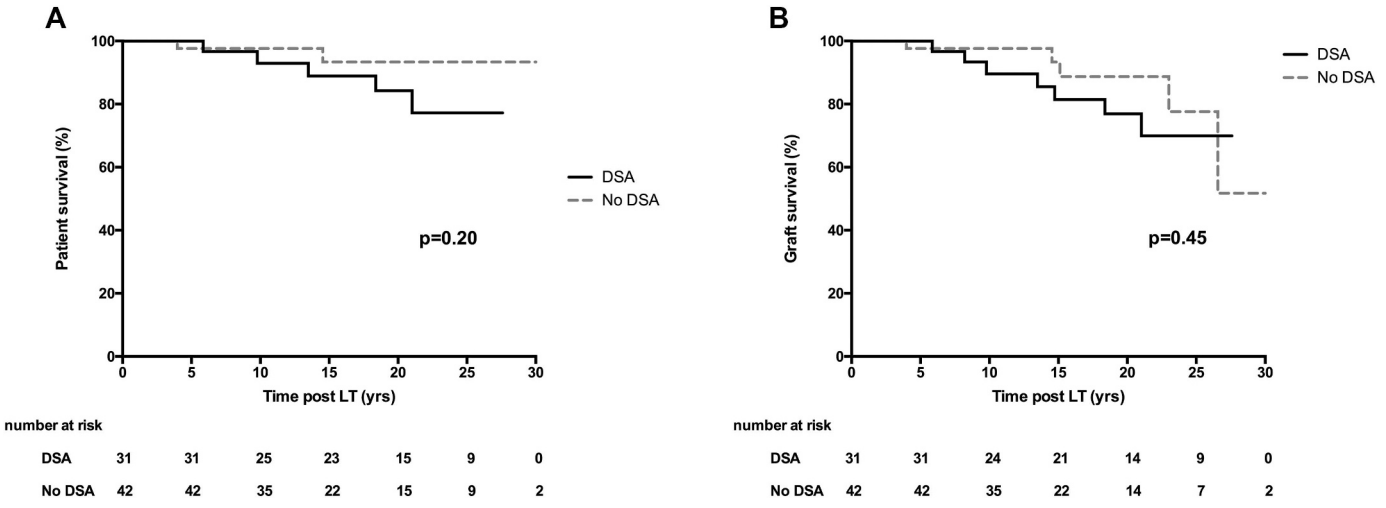

Fig. 1. Patient (A) and graft (B) survival, according to the presence of DSA (no significant difference, Logrank test, Kaplan-Meier estimates).
(A) The probability of patient survival was 97.6%, 97.6%, 93.4%, 93.4% and 93.4% at 5, 10, 15, 20 and 25 years, respectively, for patients without DSA, *vs.* 100.0%, 92.9%, 88.9%, 84.2% and 77.2% at 5, 10, 15, 20 and 25 years, respectively, for patients with DSA (p = .20).
(B) The probability of graft survival was 97.6%, 97.6%, 93.4%, 88.7% and 77.6% at 5, 10, 15, 20 and 25 years, respectively, for patients without DSA, *vs.* 100.0%, 89.6%, 81.5%, 76.9% and 69.9% at 5, 10, 15, 20 and 25 years, respectively, for patients with DSA (p = .45).

DSA formation, while a calculated MELD score > 15 at the time of LT and recipient age > 60 years old reduced the risk.

Our results strongly support that pregnancy could play a major role in DSA-mediated rejection after LT. This is probably rare since young women able to become pregnant after LT are in very limited number. One of our unfavourable cases seems to be caricatural since the woman was transplanted with a liver graft from a living donor, her husband. Such cases of accelerated rejection following offspring-to-mother and husband-to-wife transplants have been previously reported [28]. Rebibou et al. reported that about 50% of women develop anti-HLA antibodies after 3 pregnancies [29].Interestingly, Ayna et al. studied DSA in the sera of patients planned for living kidney transplantation from their spouse or children [30]. The study population included 37 wives (group I) and 48 husbands (group II). Among group I were 48.6% of positive cross-match *vs.* 10.4% for group II (p = .001). In addition, anti-HLA antibodies were detected in 94.4% of the patients with positive cross-match in group I *vs.* 60% among group II. Honger et al. investigated the frequency and determinants of pregnancy-induced child-specific sensitization shortly after full-term delivery of 301 non transplanted mothers and their children [31]. The overall frequency of pregnancy-induced sensitization ranged between 45% (MFI > 1000 cut-off) and 76% (ratio cut-off). The rate of child-specific sensitization at the HLA-A/B/C/DRB1 loci was between 28% (MFI > 1000 cut-off) and 38% (ratio cut-off). The number of live birth was associated with a higher frequency of sensitization. There was a clear hierarchy of sensitization among the investigated loci (B-locus: 31%; A-locus: 26%; DRB1-locus: 20%; C-locus: 15%; p < .0001). Some mismatched paternal HLA-antigens led to a significantly higher rate of sensitization than the average (*e.g.* HLA-A2, HLA-B49, HLA-B51, HLA-C*15). We cannot investigate this effect because we did not obtain the father's typing in most cases. When we got it, we showed that common HLA Ag between father and graft is an additional factor to develop DSA and antibody mediated rejection after pregnancy [32]. Furthermore, the mother's own HLA-phenotype (especially HLA-A/B homozygosity) was also associated with a higher rate and broadness of sensitization. The number of mismatched HLA-A/B/C eplets between both parents, strongly correlated with the rate of child-specific class I sensitization. Interestingly, it has recently been suggested, in kidney transplantation, that pregnancy-induced DSA could be more reactive than antibodies induced by prior transplantation [33]. In addition to the role of pregnancy, we confirm herein that younger age is also a predictive factor for DSA development. For instance, we reported a rate of 33.0% 10-years after LT in pediatric recipients, *vs.* 19.5% in adults [23,27]. We were not able to investigate the role of non-adherence to immunosuppressive treatment, but it has been strongly demonstrated that younger recipients (especially adolescents) of organ transplant have higher risk to be non-adherent [34–36]. In summary, the high incidence of *de novo* DSA in our population could be due to a long follow-up, the young age of our patients (including pediatric recipients), non-adherence (associated with younger age), and also the high rate of pregnancies.

Since the diagnosis of DSA-mediated rejection can be highly suspected from clinical, biological, immunological and histological features, the question of adapted treatment is the major goal, and is matter of debate. Reports of different protocols and regimens have been published, each with different outcomes and sometimes contradictory findings. In the past recent years, multiple reports using IVIG, rituximab and plasmapheresis, as single agents or in combination, have emerged [37]. Nevertheless, very few data are available in LT recipients, reported as individual cases [38–40]. We used such therapy in 4 severe cases of AMR we observed, and the outcome was favourable in 3. In one case, improvment was partial probably because of severe liver damage and pre-existing cirrhosis, leading to the indication of retransplantation, but the patient died before retransplantation. Probably, the treatment should be started as soon as possible in order to prevent irreversible liver graft lesions.

Finally, our study has some limitations. First, except in some rare cases of husband living donors, HLA grouping of children's fathers was not available, to confirm that father and graft had some common antigens associated with DSA. The determination of the HLA of the father before pregnancy could better inform the woman about the possible impact of pregnancy on the risk of developing DSA. Second, regarding the retrospective nature of our study, we cannot exclude that some pregnancies (only miscarriages or interrupted pregnancies) have not been recognized. Third, we cannot be sure that DSA appeared after pregnancy since we have not systematic DSA screening both before and after pregnancy. Nevertheless, the difference we observed between women with history of pregnancy *vs.* not (71.0 *vs.* 26.2%) strongly supports the major impact of pregnancies. Recalling the design of our study, Hebral et al. analyzed 61 pregnancies that occurred in 46 kidney transplanted women [41]. *De novo* DSA were detected after only 5.9% of pregnancies, but 27.0% of the women had DSA before pregnancy.

In conclusion, DSA-medited rejection is probably a rare but well recognized entity in LT recipients. Close monitoring of at risk patients should be recommended, including young women after pregnancy.

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