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Impact of immunosuppressive strategies on post kidney transplantation thrombocytopenia

Valentine Gierczak

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Année 2020

**IMPACT OF IMMUNOSUPPRESSIVE STRATEGIES ON POST KIDNEY
TRANSPLANTATION THROMBOCYTOPENIA**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Valentine GIERCZAK

[Données à caractère personnel]

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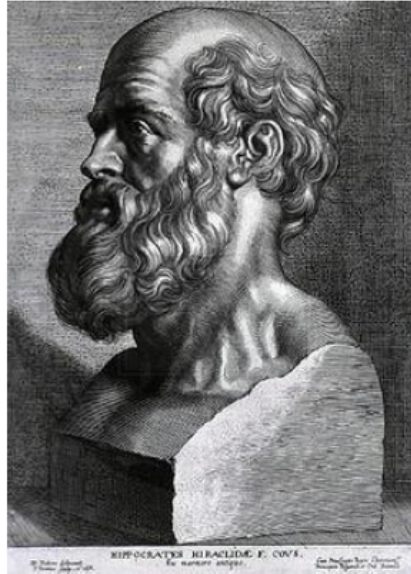
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En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

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ABSTRACT

IMPACT OF IMMUNOSUPPRESSIVE STRATEGIES ON POST KIDNEY TRANSPLANTATION THROMBOCYTOPENIA

Background: Thrombocytopenia after kidney transplantation is a common complication partly induced by immunosuppressive therapies. It might be responsible for serious hemorrhages and compromise graft and patient survival. We assessed the incidence of post transplantation thrombocytopenia in four immunosuppressive regimens as well as post transplantation safety and efficacy.

Methods: In this observational single-center retrospective study, we included all recipients who received rabbit antithymocyte globulin induction, either Thymoglobulin® (THY) or Grafalon® (GRA), and maintenance therapy which consisted in either Mycophenolate Mofetil (MMF) or Everolimus (EVR), associated with Tacrolimus and corticosteroids. Thrombocytopenia was defined as platelet count of less than 150 000 per cubic millimeter.

Results: Between 27th of July 2016 and 7th of September 2018, 237 recipients were included and 64.6% of them experienced thrombocytopenia within the first week. Thrombocytopenia was significantly more frequent ($p=0.004$) among GRA-treated patients (73.4%) compared to THY-treated patients (61.3%). These patients also had lower nadir platelet count (120 ± 52 G/l vs. 142 ± 48 G/l; $p=0.002$) and lower platelet count at discharge (227 ± 94 G/l vs. 243 ± 92 G/l; $p=0.249$). The GRA-EVR group had worse rate of thrombocytopenia (81.0% vs. 61.4%, 60.9% and 69.8% in THY-MMF, THY-EVR and GRA-MMF groups; $p=0.081$) and worse nadir platelet count (109 ± 41 G/l vs. 141 ± 47 G/l, 145 ± 52 G/l and 125 ± 56 G/l; $p=0.011$) but GRA was the only risk factor of thrombocytopenia in multivariate analyses ($p=0.002$). Rates of hemorrhages, red blood cell transfusions and reoperation within the first week as well as rates of delayed graft function, acute rejection, graft loss and death did not differ between groups after a mean time of follow-up of 25 ± 8 months.

Conclusion: It is of clinical interest that GRA associated with EVR led to more frequent and severe thrombocytopenia although there was no significant clinical consequence in this study.

Key words: Thrombocytopenia, Kidney transplantation, ATG

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INTRODUCTION

La transplantation rénale est le traitement de choix de l'insuffisance rénale terminale. Le choix du traitement immunosuppresseur après transplantation est stratégique puisque ce dernier doit assurer la survie du greffon, notamment en prévenant la survenue d'un rejet, tout en limitant la survenue d'effets secondaires. Le schéma d'immunosuppression est constitué d'un traitement d'induction et d'un traitement d'entretien. Le traitement d'induction comprend soit Basiliximab, un anticorps monoclonal non-déplétant dirigé contre le récepteur de l'interleukine 2 (CD25) à la surface des lymphocytes T, soit des immunoglobulines de lapin anti-thymocytes (ATG), anticorps polyclonaux déplétants les lymphocytes. Les ATG ont prouvé leur supériorité par rapport au Basiliximab en diminuant le risque de rejet aigu et d'apparition d'anticorps spécifiques anti-donneur chez les receveurs modérément à fortement immunisés (1–5). Dans les études, les ATG entraînaient plus de thrombopénie après transplantation que Basiliximab (2,3). Bien que cette thrombopénie soit modérée et corrigée en quelques jours, celle-ci peut favoriser la survenue de complications hémorragiques sévères précoces chez ces patients à risque hémorragique non négligeable dû à l'insuffisance rénale terminale.

Les deux ATG utilisés en pratique sont Thymoglobulin® (THY) (Sanofi-Aventis) et Grafalon® (GRA) (Neovii). Ces anticorps polyclonaux sont dérivés du lapin après immunisation par des thymocytes humains à partir de fragments de thymus prélevés en chirurgie cardiaque (THY) ou par des cellules de la ligne Jurkat, c'est-à-dire des lymphocytes T humains immortalisés issus d'une tumeur lymphoblastique T (GRA). Puisque leur source d'immunisation est différente, ces deux agents ont des profils d'élimination, de concentration en anticorps et de cibles antigéniques différents (6,7) et par conséquent, des effets secondaires et des répercussions cliniques potentiellement différents. Par exemple, il semblerait que GRA conduise à plus de thrombopénie que THY, cette thrombopénie étant aussi plus marquée, et à une utilisation plus fréquente d'érythropoïétine recombinante (8,9).

Concernant le traitement immunosuppresseur d'entretien, l'association Tacrolimus, Mycophenolate Mofetil (MMF) et corticostéroïdes est devenu un régime d'immunosuppression standard depuis l'essai ELITE-SYMPHONY (10). Cependant, les inhibiteurs de calcineurine tel que le Tacrolimus participent à la survenue de néphropathie chronique d'allogreffe, à l'origine d'une dysfonction et de la perte du greffon (11,12). C'est pourquoi l'utilisation d'un inhibiteur de mTOR (mammalian target of Rapamycin) est intéressante puisqu'elle permet de réduire la dose de Tacrolimus (5,13,14) contrairement au MMF, qui associé à des doses réduites de Tacrolimus s'avérait délétère pour la survie du greffon (15). Dans l'essai prospectif TRANSFORM, l'EVR conduisait en revanche à plus de thrombopénie que le MMF (16).

La plupart des études comparant EVR et MMF étaient associées au Basiliximab en traitement d'induction. Et les études comparant GRA et THY comportaient un traitement d'entretien par MMF. Finalement, aucune étude n'a comparé les deux ATG lorsque ces derniers sont associés à l'EVR.

Puisque GRA et EVR semblent être les plus pourvoyeurs de thrombopénie après transplantation rénale, le but de notre étude était de comparer l'incidence de la thrombopénie sous 4 schémas d'immunosuppression (THY-MMF, THY-EVR, GRA-MMF et GRA-EVR), ses conséquences cliniques et plus globalement, la survie du greffon et du patient.

INTRODUCTION

Kidney transplantation is the best treatment of end stage renal disease, offering a survival benefit in comparison with dialysis maintenance. One of the key challenges is to define the best immunosuppressive strategy to ensure good graft and patient survival by prevention of graft rejection and protection from treatment side effects. It has been the main objective of many prospective studies and the balance between efficacy and safety is tricky. Currently, post-kidney transplantation immunosuppressive strategy includes antibody induction therapy and long-term maintenance therapy. Induction agents largely used for the prevention of graft rejection after kidney transplantation are Basiliximab, a T-cell non-depleting monoclonal antibody against the interleukin-2 receptor (CD25), and Antithymocyte Globulin (ATG), T-cell depleting polyclonal antibodies from rabbit. ATG has shown its superiority over Basiliximab in terms of efficacy outcomes such as acute rejection and development of *de novo* donor specific antibodies (DSA) among recipients at moderate-to-high immunological risk (1–5). As for safety outcomes, thrombocytopenia seems more frequent among patients who received ATG than among those who received Basiliximab within the first days post-transplantation (2,3). Although thrombocytopenia was mild and transient, it might be a concerning side effect as it may worsen a perioperative coagulation imbalance in patients whose bleeding control is already compromised due to end-stage kidney disease and may lead to severe hemorrhages.

The two ATGs preparations used in clinical practice are Thymoglobulin® (THY) (Sanofi-Aventis) and Grafalon® (GRA) (Neovii). They are polyclonal immunoglobulin G preparations obtained from rabbits immunized either with human thymocytes from thymus fragments of donors undergoing cardiac surgery (THY) or with human T-cell line Jurkat (GRA). Jurkat cells are an immortalized line of human T lymphocyte cells derived from a lymphoblastic tumor. Due to differences in the immunization source, these products have different clearance, antibody concentration and antigen profile (6,7). Moreover, recommended doses of ATG are

higher for GRA than for THY. These differences may have relevant clinical consequences, and little is known about their clinical equivalence. Notably, GRA has been reported to be associated with more frequent and pronounced cytopenia immediately after transplantation than THY, leading to more frequent use of erythropoietin-stimulating agent therapy (8,9) without any difference of graft function.

As for maintenance therapy, the combination of Tacrolimus, Mycophenolate Mofetil (MMF) and corticosteroids has become a standard of immunosuppressive therapy after kidney transplantation since the ELITE-SYMPHONY trial (10). However, calcineurin inhibitor-related nephrotoxicity is a major risk factor of chronic allograft nephropathy and late graft dysfunction and loss (11,12). The use of mammalian target of Rapamycin inhibitors such as Everolimus (EVR) instead of MMF seems to be a promising strategy as it has shown comparable immunosuppressive efficacy when associated to reduced doses of calcineurin inhibitors (5,13,14). Of note, Tacrolimus minimization in association with MMF was detrimental to graft survival (15). In the randomized international TRANSFORM trial, EVR-treated patients experienced statistically more thrombocytopenia within the first-year post transplantation than MMF-treated patients (16).

Nevertheless, most studies comparing EVR and MMF included patients receiving an induction therapy with Basiliximab and not with ATG. And all studies comparing GRA and THY were based on MMF-associated regimens. Notably, no study has yet compared the two commonly used ATGs when associated with EVR.

As GRA and EVR have both been reported to be associated with more frequent thrombocytopenia, the aim of our retrospective study was to compare the incidence of post-transplant thrombocytopenia and its clinical consequences in four Tacrolimus-associated immunosuppressive strategies: THY plus MMF (THY-MMF), THY plus EVR (THY-EVR), GRA plus MMF (GRA-MMF) and GRA plus EVR (GRA-E). Safety and efficacy after kidney transplantation of these strategies were also assessed.

METHODS

- Study design and population

This observational single-center retrospective study was conducted in the Nephrology and Kidney Transplantation department of the Grenoble-Alpes University Hospital, France. All consecutive kidney transplant recipients aged ≥ 18 years old from living or deceased donor between 27th of July 2016 and 7th of September 2018 were included. Patients were excluded if they were desensitized for ABO or HLA incompatible transplantation or if they received simultaneous dual organ transplantation. Based on their induction and maintenance immunosuppressive therapy, patients were divided into 4 groups: THY-MMF, THY-EVR, GRA-MMF and GRA-EVR. All patients provided written and informed consent to the anonymous use of their medical data. The electronic medical records of the hospital were used to collect demographic data on recipients and donors. All medical data were collected from our database [CNIL (French national committee for data protection) approval number 1987785v0] between the 1st and the 30th of September 2019.

- Immunosuppressive therapy

The immunosuppressive therapy including induction therapy and maintenance therapy was decided at the discretion of the medical team prior to transplantation. Induction therapy with rabbit ATG (THY or GRA) was initiated intraoperatively before graft reperfusion. For non-HLA-sensitized recipients, induction included either THY (0.5 mg/kg/d for 5 days) or GRA (3 mg/kg/d for 3 days). For HLA-sensitized recipients, induction consisted in THY at the dose of 0.75 to 1mg/kg/d for 5 days. The maintenance immunosuppressive therapy consisted in corticosteroids, Tacrolimus, and either MMF or EVR. 500 mg of intravenous Methylprednisolone were administered on day 0 before surgery and then tapered to 10mg per day of oral Prednisone by day 7. Corticosteroids were withdrawn at month 3 except for

recipients who experienced biopsy-proven acute rejection or in the presence of Donor Specific Antibodies (DSA). In diabetic recipients at low immunological risk of rejection recipients, corticosteroids were withdrawn on day 4. MMF doses were 2g per day reduced to 1g per day after 2 weeks post transplantation. When associated with MMF, Tacrolimus was initiated on day 4 and doses were adjusted to reach drug trough concentration of 8-12 ng/ml within the first month and 5-8 ng/ml afterwards. EVR was initiated on day 1 and doses were adjusted to reach drug trough concentration of 4-6 ng/ml within the first month and 5-7 ng/ml afterwards. When associated with EVR, Tacrolimus was initiated on day 1 and doses were adjusted to target drug trough concentration of 5-6 ng/ml within the first month and 3-4 ng/ml afterwards.

- Concomitant therapy

Cytomegalovirus (CMV) prophylaxis consisted in oral Valganciclovir starting on day 4 except for CMV seronegative recipients receiving from CMV seronegative donors and recipients receiving EVR as maintenance therapy. Doses were adjusted to the estimated Glomerular Filtration Rate (eGFR). All recipients received *Pneumocystis jiroveci* prophylaxis with oral Sulfamethoxazole-Trimethoprim from day 4. Oral proton-pump inhibitor Esomeprazole at 20 mg per day was also administered until corticosteroids were stopped.

- Primary and secondary endpoints

The primary endpoint was the incidence of thrombocytopenia within the first week post transplantation defined as platelet count of less than 150 000 per cubic millimeter. Secondary endpoints included the assessment of the nadir platelet count defined as the lowest platelet count during the first week, and the assessment of the platelet count at discharge. We also assessed the incidence of clinically relevant hemorrhage, red blood cell transfusion and reoperation within the first post-transplant week. Clinically relevant hemorrhage included hematoma diagnosed by ultrasound or computerized tomography scan and externalized bleeding.

Efficacy of transplantation included the assessment of renal function at month 12 and at last available measurement, the incidence of delayed graft function, acute rejection, graft loss and death at last follow-up. Renal function was evaluated by serum creatinine concentration and estimated Glomerular Filtration Rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. Delayed graft function was defined as the need for dialysis within the first post-transplant week. All suspected acute rejections were confirmed by biopsy according to the 2013 and 2015 Banff classifications (17,18). Protocol biopsies were also performed systematically at month 3 post transplantation. Borderline rejection (Banff category 3) was designated as biopsy-proven acute rejection.

- Statistical analysis

Symmetrically distributed variables are shown as their means \pm standard deviations. For a heterogeneous distribution, variables are shown as the median [inter-quartile range]. Categorical variables are expressed as a percentage. Student's t-test or the Mann-Whitney U test was used to compare continuous variables. The chi-square test was used to compare categorical variables. To evaluate factors associated with nadir platelet counts, an ANOVA logistic regression with multivariable analysis was used. Kaplan Meier test assessed patient and graft survival as well as acute rejection free survival. A p-value of <0.05 was considered to be statistically significant. Analyses were performed using R software (19).

RESULTS

- Population

Between 27th of July 2016 and 7th of September 2018, 274 patients were kidney transplanted in the Nephrology and Kidney Transplantation department of the Grenoble-Alpes University Hospital. Twenty-five were excluded because of ABO or HLA incompatible transplantation requiring desensitization prior to transplantation. We also excluded 10 patients because of post-operative acute venous thrombosis resulting in transplantectomy within the first 72 hours after transplantation, 1 patient because of acute aortic dissection leading to death on day 6 and 1 patient who underwent plasmapheresis because of a suspected relapse of focal segmental glomerulosclerosis on day 1. In the end, 237 patients were retrospectively included in our analyses.

Induction therapy consisted in either THY at a mean total dose of 4.0 ± 1.4 mg/kg or GRA at a mean total dose of 9.6 ± 2.4 mg/kg. The mean daily dose of Tacrolimus was 6.2 ± 2.8 mg at discharge. For THY-MMF and GRA-MMF treated recipients, the mean daily dose of MMF at discharge were respectively 1745 ± 462 mg and 1733 ± 467 mg. For THY-EVR and GRA-EVR treated recipients, the mean daily dose of EVR at discharge were respectively 4.0 ± 2.2 mg and 4.6 ± 1.5 mg. Baseline characteristics of the 4 groups at the time of transplantation are reported in table 1.

The principal nephropathies were chronic glomerulonephritis (27%), undefined nephropathy (16%), hypertension (13.1%), polycystic kidney disease (12.7%), diabetes mellitus (9.3%) and interstitial nephropathy (9.3%). The mean time of follow-up was 25 ± 8 months [2 to 39 months].

- Primary endpoint

Within the first week, thrombocytopenia occurred more frequently in the GRA-EVR group than in the THY-MMF group, the THY-EVR group and the GRA-MMF group although not significantly: respectively 81.0% vs. 61.4%, 60.9% and 69.8%; $p=0.081$. The nadir platelet count in the GRA-EVR group was significantly lower than the other groups: 109 ± 41 G/l vs. 141 ± 47 G/l for the THY-MMF group, 145 ± 52 G/l for the THY-EVR group and 125 ± 56 G/l for the GRA-MMF group; $p=0.011$ (figure 1). Figure 2 illustrates the distribution of nadir platelet count in the 4 groups according to platelet count ranges: above 150 G/l, from 100 to 149 G/l, from 50 to 99 G/l and below 50 G/l.

In univariate analyses, there was a significant association between thrombocytopenia and the ATG use: GRA-treated patients experienced more frequent thrombocytopenia than THY-treated patients (respectively 73.4% vs. 61.3%; $p=0.004$). Thrombocytopenia was more pronounced for GRA-treated patients with a significant lower nadir platelet count than THY-treated patients (respectively 120 ± 52 G/l vs. 142 ± 48 G/l; $p=0.002$). Platelet count at discharge was lower although not significantly (respectively 227 ± 94 G/l for GRA-treated patients vs. 243 ± 92 G/l for THY-treated patients; $p=0.249$). In a logistical regression multivariate ANOVA model, the association of EVR with GRA did not reach significance for the nadir platelet count: GRA was associated with a significant lower nadir platelet count compared to THY ($p=0.002$) but not when GRA was associated with EVR ($p=0.257$). Regarding platelet counts at discharge, multivariate analyses did not show any significant correlation with ATG use ($p=0.249$) neither with EVR use ($p=0.395$).

Finally, we assessed the ability for patients to recover from thrombocytopenia. Recovery of platelet was defined as the difference between platelet count at discharge and nadir platelet count. Recovery of platelet was not statistically different between groups in univariate and multivariate analyses: increase of 104 ± 79 G/l in THY-MMF group, 89 ± 66 G/l in THY-EVR group, 114 ± 64 G/l in GRA-MMF and 93 ± 70 G/l in GRA-EVR ($p=0.515$). However, it is

noteworthy that recovery of platelet tended to be less effective with EVR-associated regimens compared to MMF-associated regimens ($p=0.085$) and was significantly less effective in living donor ($p=0.044$).

Although not significantly, the platelet count at discharge remained lower than the pre-transplant platelet count in the GRA-EVR group: 202 ± 94 G/l at discharge vs. 233 ± 65 G/l before transplantation ($p=0.087$). In the THY-MMF, THY-EVR and GRA-EVR groups, the platelet count at discharge was higher than the pre-transplant platelet count (figure 3).

- Secondary endpoints

Since the administered dose of THY was different between non-HLA-sensitized and HLA-sensitized patients, we assessed whether the dose of THY may influence the incidence of thrombocytopenia within the first week. The nadir platelet count was similar between the 3 subgroups of THY-treated patients: 147 ± 60 G/l for the low dose group (less than 2.5 mg/kg [$n=20$]), 144 ± 46 G/l for the moderate dose group (between 2.5 and 3.75 mg/kg [$n=70$]) and 140 ± 47 G/l for the high dose (more than 3.75 mg/kg [$n=83$]); $p=0.768$ (figure 4).

Just as the incidence of thrombocytopenia within the first week was not statistically different between the 4 groups, the incidence of clinically relevant hemorrhages, red blood cell transfusion and reoperation within the first week were similar between groups: respectively $p=0.164$, $p=0.147$ and $p=0.583$. However, length of hospital stay in the GRA-EVR group was 8.1 ± 2.2 days, significantly shorter compared to the other groups; $p=0.039$ (table 2).

Univariate analyses also did not show any difference between groups in rate of delayed graft function (15% in THY-MMF group, 8.7% in THY-EVR group, 11.6% in GRA-MMF group and 4.8% in GRA-EVR group; $p=0.471$), biopsy-proven acute rejection (11.8% in THY-MMF group, 13% in THY-EVR group, 16.3% in GRA-MMF group and 4.8% in GRA-EVR group; $p=0.616$), death-censored graft loss (0.8% in THY-MMF group, 2.2% in THY-EVR group, 2.3% in GRA-MMF group and 0% in GRA-EVR group; $p=0.755$) and death (6.3% in THY-

MMF group, 2.2% in THY-EVR group, 4.7% in GRA-MMF group and 0% in GRA-EVR group; $p=0.486$) at last follow-up.

Consistent with these results, mean serum creatinine level at month 12 was comparable between groups: $130.3 \pm 46.6 \mu\text{mol/l}$ for THY-MMF group, $140.3 \pm 36.4 \mu\text{mol/l}$ for THY-EVR group, $129.8 \pm 40.8 \mu\text{mol/l}$ for GRA-MMF group and $113.1 \pm 29.3 \mu\text{mol/l}$ for GRA-EVR group ($p=0.116$) as well as mean eGFR: respectively $61.1 \pm 24.3 \text{ ml/min}$, $53.4 \pm 17.4 \text{ ml/min}$, $61.1 \pm 22.4 \text{ ml/min}$ and $71.9 \pm 29.9 \text{ ml/min}$ ($p=0.228$). Comparison of serum creatinine level and eGFR at last available measurement also showed similar results: no statistical difference in mean serum creatinine level ($129.9 \pm 44.4 \mu\text{mol/l}$ in THY-MMF group, $145.0 \pm 58.2 \mu\text{mol/l}$ in THY-EVR, $142.9 \pm 57.1 \mu\text{mol/l}$ in GRA-MMF group and $107.9 \pm 24.0 \mu\text{mol/l}$ in GRA-EVR group; $p=0.771$) and mean eGFR (respectively $60.7 \pm 24.4 \text{ ml/min}$, $54.5 \pm 20.3 \text{ ml/min}$, $57.5 \pm 24.7 \text{ ml/min}$ and $74.4 \pm 28.5 \text{ ml/min}$; $p=0.264$).

Finally, we assessed the impact of thrombocytopenia on graft and patient survival. Kaplan Meier survival analyses demonstrated that the risk of biopsy-proven acute rejection, graft loss and death were similar between recipients with thrombocytopenia and recipients without thrombocytopenia: respectively $p=0.500$ (figure 5), $p=0.190$ (figure 6) and $p=0.059$ (figure 7). We also compared rejection free, graft and patient survival between the 4 groups including the early post-transplant failures such as post-operative acute venous thrombosis resulting in transplantectomy. There was not a significant between-group difference in the Kaplan Meier survival analyses (supplementary figure 8).

DISCUSSION

Thrombocytopenia after kidney transplantation is a common complication which may be induced by immunosuppressive therapies and should not be underestimated because of potential severe consequences. Particular attention should be held in the critical early post-transplant period.

This retrospective study comparing 4 immunosuppressive regimens after kidney transplantation revealed differences regarding the incidence of thrombocytopenia. GRA plus EVR treated patients experienced more frequent thrombocytopenia although not significantly compared to patients receiving other treatments: THY and MMF, and thrombocytopenia was significantly more pronounced. These results are consistent with previous studies reporting that EVR is associated with more frequent thrombocytopenia compared to MMF (5,16) as well as GRA compared to THY (8,9).

Burkhalter et al. reported a lower platelet count on day 1 and 7 in GRA-treated patients compared to THY-treated patients. On day 14, platelet counts were normalized and did not differ between the groups (8). In a study of Rostaing et al., platelet counts had normalized by day 7 in the THY induction group and by day 10 in the GRA induction group (9). In our study, platelet counts were also normalized at discharge but the platelet count still remained lower at discharge in the GRA-EVR compared to the other groups. We have to consider for these results that the length of hospital stay was shorter in the GRA-EVR group: 8.1 days versus 9.9 to 12.2 days in the other groups, and there might have been no absolute difference in platelet count by day 14.

Thrombocytopenia is common after kidney transplantation, but its incidence depends on the chosen threshold of platelet count. The overall incidence of thrombocytopenia in our population was high (64.6%) and the thrombocytopenia definition of a platelet count < 150 G/l is questionable because it might not significantly increase the bleeding risk. Nevertheless, almost

one third of the recipients required red blood cell transfusion (30.4%). Although post-transplant anemia is multifactorial (20), it has been associated with graft loss and mortality (21,22). Clinicians should not omit any contributing factor of anemia such as thrombocytopenia and the subsequent increased bleeding risk.

More than half of the recipients in GRA-EVR group had a nadir platelet count between 50 and 99 G/l. Although no statistical difference was found between groups using the cut-off platelet count of 150 G/l to define our primary endpoint, this suggests that there might have been a significant difference if we had considered a lower cut-off platelet count. We therefore assessed the incidence of thrombocytopenia below the platelet count cut-off of 130 G/l and statistical difference was reached.

Thrombocytopenia appears rapidly within the first days after transplantation: some studies report lowest values on day 3 (9,23) and platelet counts rarely decrease below 50 G/l (24). Indeed, absolute values of platelet counts in our study were moderate: the lowest platelet count in the GRA-EVR group was 53 G/l, no patient required platelet transfusion and the incidence of clinically relevant hemorrhages and red blood cell transfusion within the first post-transplant week was comparable between the 4 groups. Unfortunately, we could not collect data about some other bleeding risk factors of recipients such as anticoagulation therapy or blood coagulation disorders. Only the age of recipients was collected and was different between the groups: recipients in the GRA-EVR group were significantly younger than the other recipients and eventually had a lower bleeding risk at baseline.

Unlike the association between EVR and thrombocytopenia (25), the physiopathology underlying ATG-induced thrombocytopenia is still unclear. Cumpelik et al. suggested a link between complement activation induced by ATG and platelet reduction (26). The mechanism explaining the reported difference of thrombocytopenia incidence between GRA and THY is also not understood. Different concentration with diverse specificity of antibodies may be responsible for such various effects (24). Most studies have investigated the effects of ATG on

leukocytes (7) but not on non-immune cells such as platelets. It is noteworthy that the effects of ATG on the immune system still remain at least one year after transplantation. Recovery of peripheral T-cell counts might be complete one year after transplantation but several studies have documented long-term effects on T-cell function (27,28). Compared to leukocyte depletion, platelet depletion may be more transient, but we do not have any knowledge about an eventual long-term effect on platelet function.

Whereas there was not any dose-dependent effect of GRA reported in the literature, several studies have reported that increased dose of THY is correlated with more frequent infections (29,30) and less effective T-cell recovery (6). In our study, platelet counts did not depend on the dose of THY.

As for efficacy outcomes, the rates of delayed graft function, acute rejection, graft loss and death did not differ between groups of treatments. But the groups were not comparable in terms of immunological risk at baseline. Indeed, patients receiving GRA plus EVR had significantly lower BMI, less diabetes mellitus background, less HLA-sensitization and less prior transplantation background, predicting best graft outcomes (31–33).

As mentioned above, the main limitation of our study relates to the quantitative and qualitative variability of patients between the groups. This is due to the retrospective design of the study and the fact that the immunosuppressive therapy was decided prior to transplantation at the discretion of the medical team.

Moreover, we did concentrate on the platelet toxicity of immunosuppressive agents but did not investigate other frequent side effects. For example, many studies have reported more CMV infections with THY compared to GRA (24,28) whereas EVR commonly has anti-viral beneficial effects (14,34), and GRA is frequently associated with more frequent anemia and use of erythropoietin-stimulating agent therapy than THY (8,9).

In conclusion, this retrospective study shows more frequent and pronounced thrombocytopenia within the first days after kidney transplantation in GRA-treated patients. Although absolute platelet counts were even lower in the GRA-EVR regimen compared to THY-MMF, THY-EVR and GRA-MMF regimens, multivariate analyses did not show a significant increased risk of EVR for thrombocytopenia. The difference in platelet counts was of no clinical relevance in our recipients but still could be of clinical interest in specific cases, especially for recipients at high bleeding risk at baseline. This should be evaluated prospectively in a larger population.

Table 1. Baseline characteristics.*

	All (n=237)	THY-MMF (n=127)	THY-EVR (n=46)	GRA-MMF (n=43)	GRA-EVR (n=21)	p-values
Recipient characteristics						
Age (years)	55.4 ± 14.9	54.7 ± 11.9	53.3 ± 19.4	63.2 ± 9.5	47.5 ± 14.5	0.003
Female - n (%)	83 (35.0)	51 (40.2)	12 (26.1)	14 (32.6)	6 (28.6)	0.310
Preemptive transplantation - n (%)	41 (17.3)	18 (14.2)	9 (19.6)	8 (18.6)	5 (23.8)	0.724
Dialysis - n (%)	196 (82.7)	108 (85.8)	37 (80.4)	35 (81.4)	16 (76.2)	0.927
Time on dialysis (days)	1175 ± 1469	1393 ± 1872	836 ± 520	973 ± 676	896 ± 577	0.138
Body-mass index (kg/m ²)	25.2 ± 4.0	25.6 ± 4.3	24.6 ± 3.0	25.0 ± 4.4	23.7 ± 3.4	0.045
Background of diabetes - n (%)	52 (21.9)	43 (33.9)	4 (8.7)	4 (9.3)	1 (4.8)	<0.001
Background of hypertension - n (%)	172 (72.6)	96 (75.6)	30 (65.2)	33 (76.7)	13 (61.9)	0.333
Pre-transplant biology						
Hemoglobin (g/l)	120 ± 14	120 ± 15	118 ± 13.5	121 ± 13.1	118 ± 17	0.755
Ferritin (mg/l)	252 ± 222	271 ± 225	228 ± 224	210 ± 231	268 ± 187	0.417
Platelets (G/l)	224 ± 64	219 ± 59	230 ± 70	229 ± 72	233 ± 65	0.564
CD3 (G/l)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.3	1.1 ± 0.6	0.9 ± 0.3	0.826
Lymphocytes (G/l)	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.4	1.4 ± 0.6	1.3 ± 0.6	0.741
Pre-transplant HLA sensitization - n (%)	47 (19.8)	36 (28.3)	8 (17.4)	3 (7.0)	0	<0.001
Donor characteristics						
Age (years)	54.1 ± 16.2	55.2 ± 15.8	55.8 ± 16.6	51.3 ± 17	48.7 ± 15.4	0.187
Donor type						
Deceased heart-beating - n (%)	154 (65.0)	85 (66.9)	31 (67.4)	23 (53.5)	15 (71.4)	0.360
Deceased non-heart-beating - n (%)	32 (13.5)	27 (21.3)	2 (4.3)	3 (7.0)	0	0.002
Living - n (%)	51 (21.5)	15 (11.8)	13 (28.3)	17 (39.5)	6 (28.6)	<0.001
Transplantation characteristics						
First transplantation - n (%)	209 (88.2)	107 (84.3)	41 (89.1)	42 (97.7)	19 (90.5)	0.048
Cold ischemia time (min)	687 ± 398	785 ± 366	577 ± 346	540 ± 442	643 ± 449	<0.001
Immunosuppressive therapy						
Thymoglobulin® - mean dose (mg/kg)	4.0 ± 1.4	4.2 ± 1.4	3.5 ± 1.4	-	-	0.001
Grafalon® - mean dose (mg/kg)	9.6 ± 2.4	-	-	10.1 ± 2.7	8.7 ± 1.3	0.026
Tacrolimus - mean dose (mg)	6.2 ± 2.8	6.9 ± 2.9	4.7 ± 2.6	6.1 ± 2.3	5.4 ± 1.9	0.611
MMF - mean dose (mg)	1742 ± 462	1745 ± 462	-	1733 ± 467	-	0.876
Everolimus - mean dose (mg)	4.2 ± 2	-	4.0 ± 2.2	-	4.6 ± 1.5	0.012

*Plus-minus values are means ± SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®.

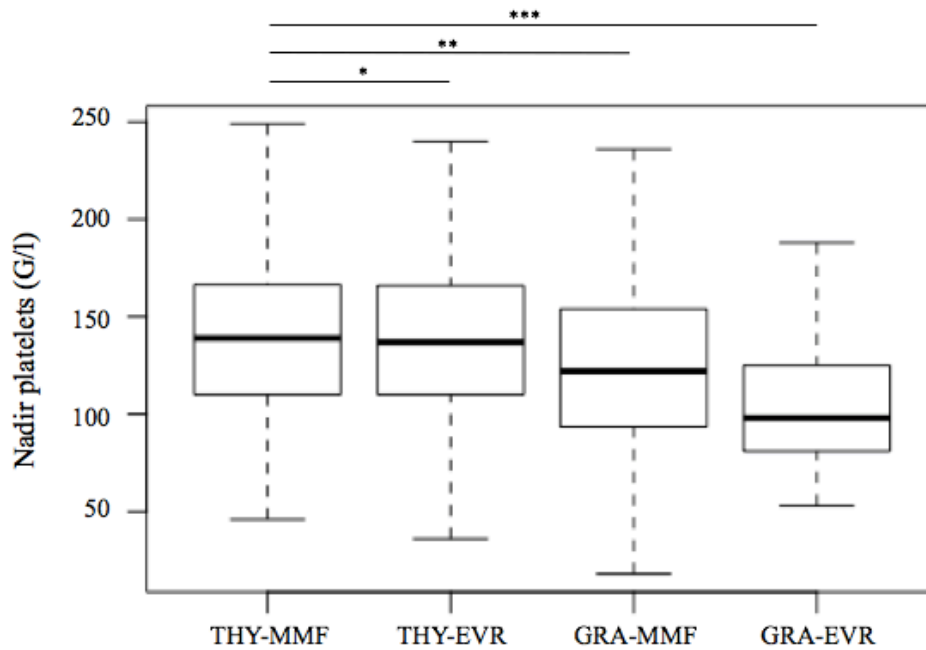


Figure 1. Nadir platelet counts of THY-MMF, THY-EVR, GRA-MMF and GRA-EVR treated patients. THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®. Nadir platelet counts of the THY-EVR and GRA-MMF groups were similar to the standard THY-MMF group (respectively * $p=0.658$ and ** $p=0.058$) whereas nadir platelet count of GRA-EVR treated patients was statistically lower than THY-MMF treated patients (** $p=0.006$).

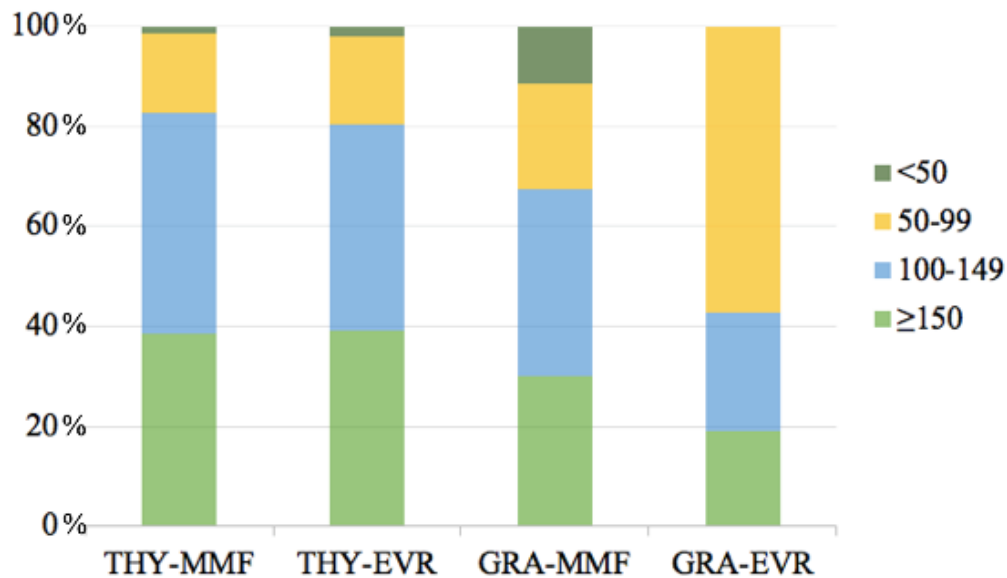


Figure 2. Distribution of nadir platelet count in THY-MMF, THY-EVR, GRA-MMF and GRA-EVR groups according to platelet count ranges: above 150 G/l, from 100 to 149 G/l, from 50 to 99 G/l and below 50 G/l. THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®.

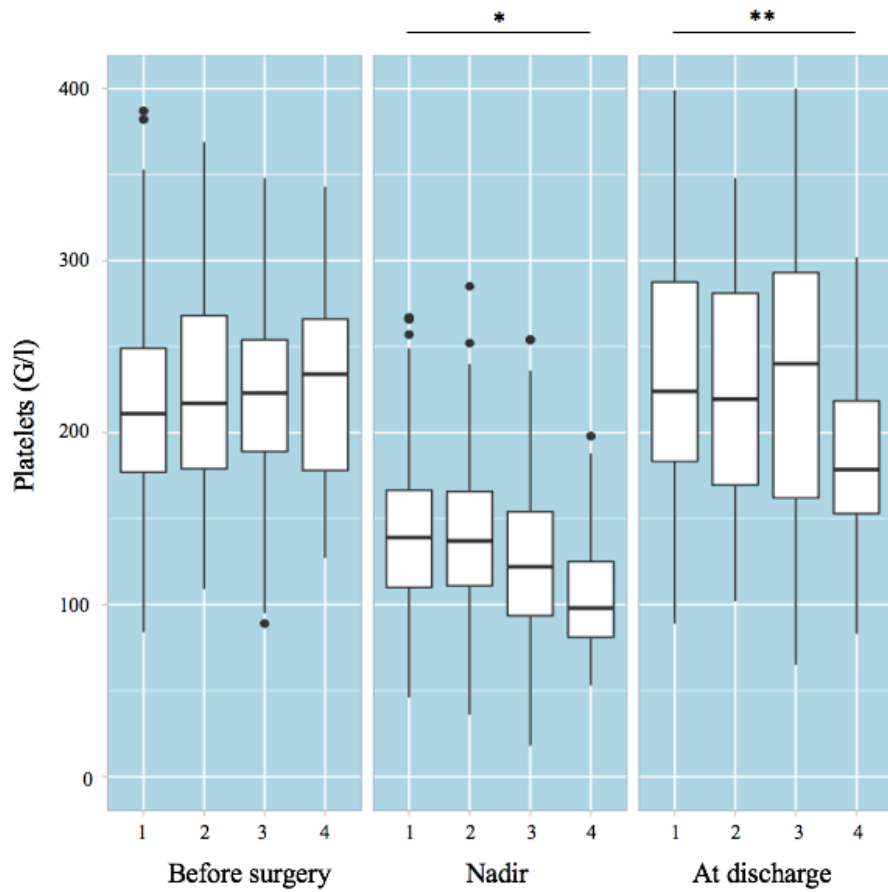


Figure 3. Platelet count before surgery, nadir platelet count and platelet count at discharge for (1) THY-MMF, (2) THY-EVR, (3) GRA-MMF and (4) GRA-EVR treated patients. THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®. Compared to the standard THY-MMF group, nadir platelet count (* $p=0.006$) and platelet count at discharge (** $p=0.047$) were significantly lower in the GRA-EVR group.

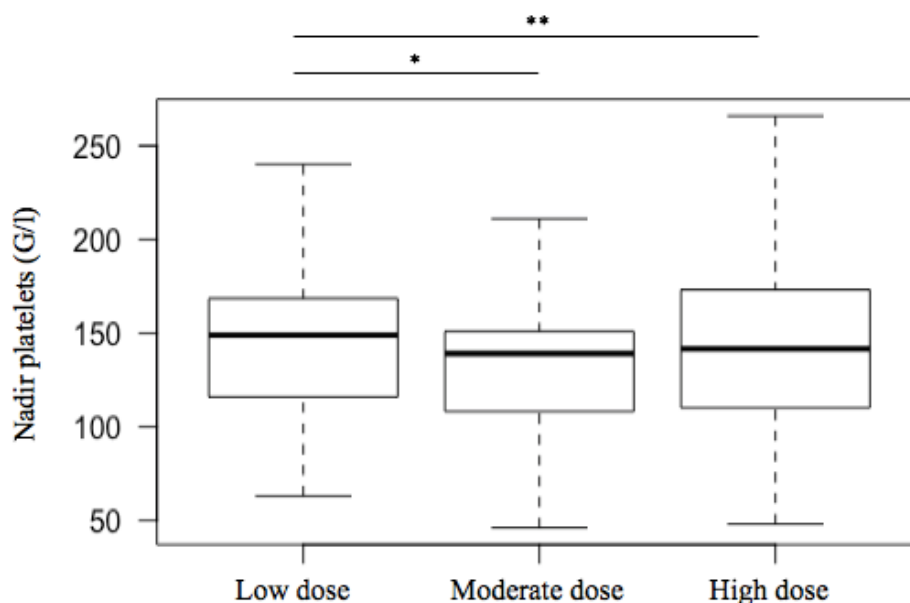


Figure 4. Nadir platelet counts within the first post-transplant week in patients treated with Thymoglobulin® at low dose (inferior to 2.5mg/kg), moderate dose (2.5 to 3.75mg/kg) and high dose (superior to 3.75mg/kg). Nadir platelet count of moderate and high dose Thymoglobulin®-treated patients were similar to low dose Thymoglobulin®-treated patients (respectively *p=0.506 and **p=0.488).

Table 2. Efficacy outcomes in univariate analyses

	All (n=237)	THY-MMF (n=127)	THY-EVR (n=46)	GRA-MMF (n=43)	GRA-EVR (n=21)	p-values
Hemorrhage - no (%)	26 (11.0)	18 (14.2)	4 (8.7)	1 (2.3)	3 (14.3)	0.164
Red blood cell transfusion - no (%)	72 (30.4)	41 (32.3)	8 (17.4)	14 (32.6)	9 (42.9)	0.137
Reoperation - no (%)	23 (9.7)	15 (11.8)	4 (8.7)	2 (4.7)	2 (9.5)	0.583
Length of hospital stay - days	10.9 ± 7.5	12.2 ± 9.3	9.9 ± 3.6	10.2 ± 5.3	8.1 ± 2.2	0.039
Delayed graft function - no (%)	29 (12.2)	19 (15.0)	4 (8.7)	5 (11.6)	1 (4.8)	0.471
Biopsy proven acute rejection - no (%)	29 (12.2)	15 (11.8)	6 (13.0)	7 (16.3)	1 (4.8)	0.616
Graft loss - no (%)	3 (1.3)	1 (0.8)	1 (2.2)	1 (2.3)	0	0.755
Death - no (%)	11 (4.6)	8 (6.3)	1 (2.2)	2 (4.7)	0	0.486

Plus-minus values are means ± SD. THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®.

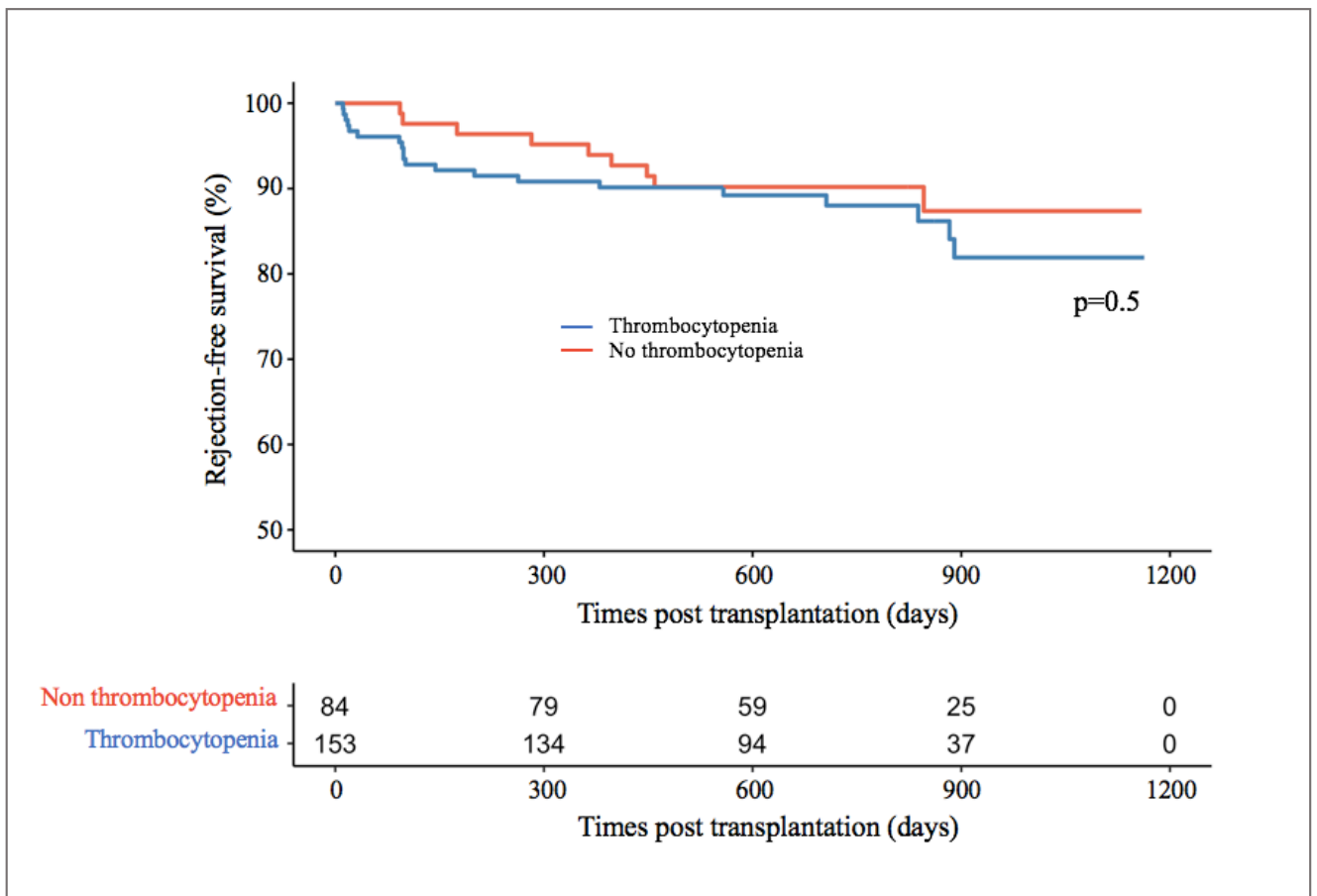


Figure 5. Rejection-free survival in patients with and without thrombocytopenia within the first post-transplant week.

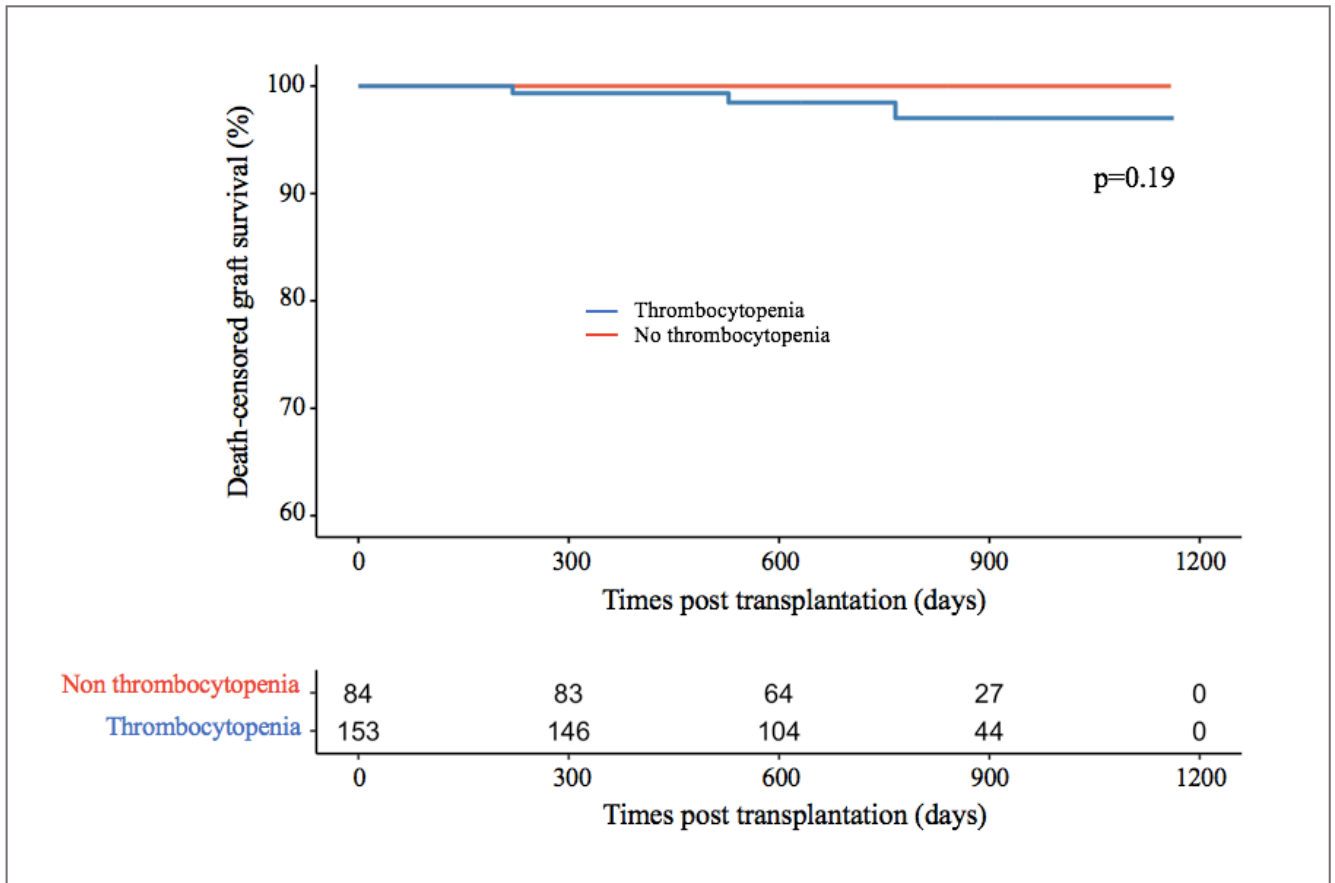


Figure 6. Death-censored graft survival in patients with and without thrombocytopenia within the first post-transplant week.

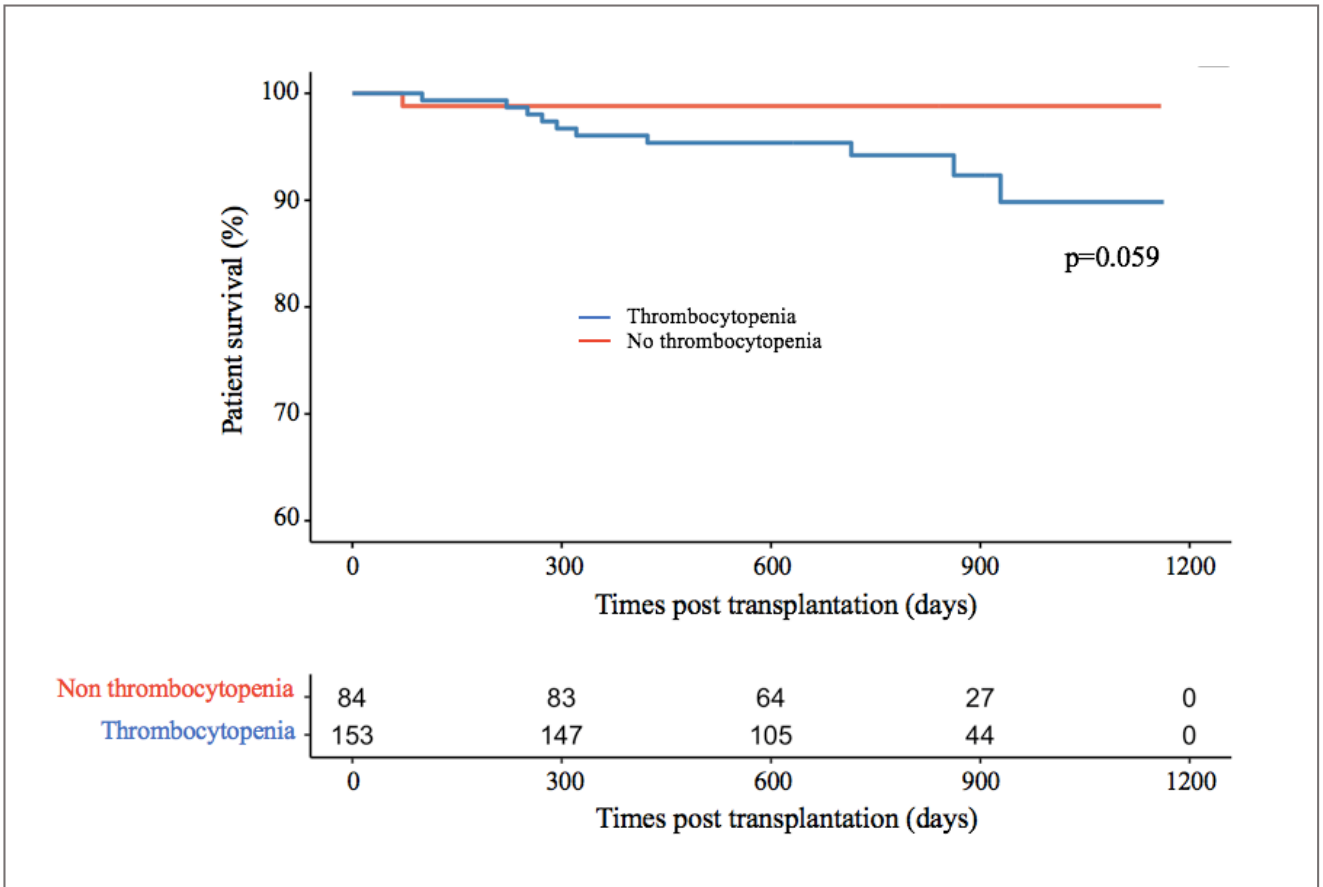


Figure 7. Patient survival in patients with and without thrombocytopenia within the first post-transplant week.

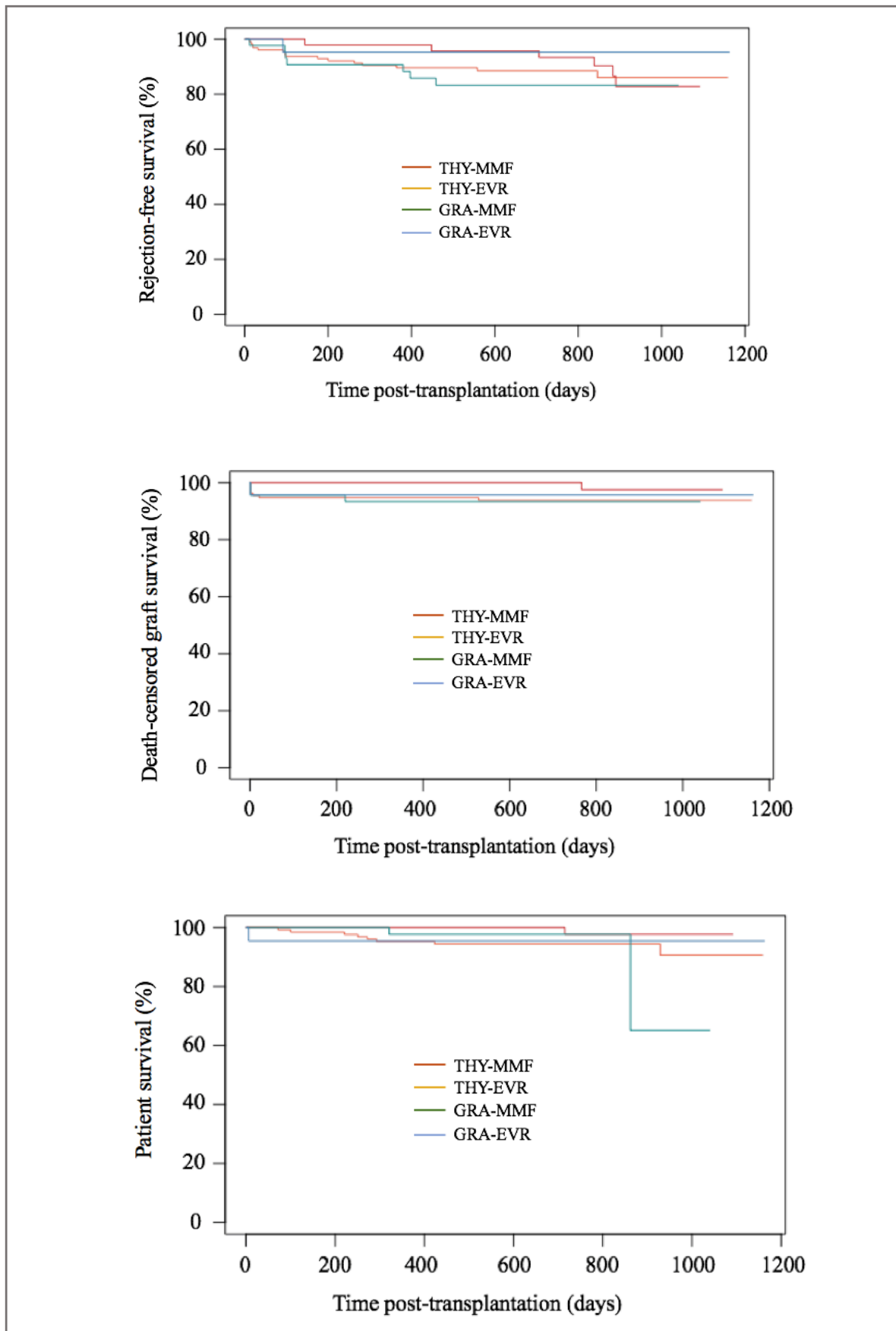


Figure 8. Rejection-free survival, death-censored graft survival and patient survival in THY-MMF, THY-EVR, GRA-MMF and GRA-EVR treated patients. THY = Thymoglobulin®, MMF = Mycophenolate Mofetil, EVR = Everolimus, GRA = Grafalon®.

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DISCUSSION ET PERSPECTIVES

La thrombopénie est une complication fréquente et précoce après transplantation rénale, pouvant être à l'origine de complications hémorragiques sévères, et favorisée par plusieurs agents immunosuppresseurs utilisés en routine clinique. L'objectif de ce travail était de comparer l'incidence de la thrombopénie sous 4 schémas d'immunosuppression. Nous avons ainsi mis en évidence que l'association du Grafalon® (GRA) en traitement d'induction associé avec Everolimus (EVR) en traitement d'entretien conduisait de manière non significative à plus de thrombopénie que les associations suivantes : Thymoglobulin® (THY) plus Mycophenolate Mofetil (MMF), THY plus EVR et GRA plus MMF. Cette thrombopénie était significativement plus importante en valeur absolue dans le groupe GRA-EVR. L'utilisation du GRA était le seul facteur de risque de thrombopénie en analyse multivariée.

Le seuil de plaquettes de 150 G/l en dessous duquel nous avons défini notre critère de jugement principal est discutable. Plus de la moitié des receveurs du groupe GRA-EVR avaient un nadir de plaquettes entre 50 et 100 G/l. En abaissant le seuil de plaquettes à 130 G/l, l'incidence de la thrombopénie chez ce groupe en comparaison aux groupes THY-MMF, THY-EVR et GRA-MMF était statistiquement significative.

La thrombopénie était rapidement corrigée à la sortie d'hospitalisation avec des valeurs de plaquettes toutefois inférieures dans le groupe GRA-EVR. De plus, les valeurs de nadir de plaquette restaient modérées, la plus basse dans le groupe GRA-EVR étant à 53 G/l. Concernant les conséquences cliniques de la thrombopénie, les receveurs ayant présenté une thrombopénie dans la première semaine après transplantation ne se sont pas plus compliqués d'hémorragies sévères ni n'ont requis plus de transfusion de culots globulaires ou nécessité de reprise chirurgicale, en comparaison aux receveurs sans thrombopénie induite. De même, les taux de reprise retardée de fonction du greffon, de rejet, de perte du greffon ou de décès étaient comparables pendant la période de suivi.

Il faut noter que les autres facteurs de risque hémorragique de nos receveurs tels que la prise de traitement anticoagulant ou les anomalies de la coagulation n'ont pas été relevés dans cette étude, ce qui a pu masquer une éventuelle différence. Dans cette période critique à haut risque hémorragique qu'est la première semaine après transplantation, lié aux perturbations de l'hémostase induites par l'insuffisance rénale terminale et la chirurgie, ce sur-risque de thrombopénie favorisé par l'association GRA plus EVR est à prendre en compte.

Notre étude possède des limites évidentes. La principale est l'extrême variabilité des patients inclus, liée au caractère rétrospectif de l'étude. Par exemple, les patients recevant un schéma GRA-EVR étaient significativement plus jeunes, donc potentiellement à risque hémorragique plus faible.

En conclusion, l'association GRA plus EVR semble être pourvoyeuse d'un sur-risque de thrombopénie qu'il ne faut pas négliger, bien que n'ayant montré aucune conséquence en pratique clinique. Peu étudiée dans la littérature, cette association présente des résultats rassurants quant à ses répercussions sur la survie du greffon et du patient.

THÈSE SOUTENUE PAR : Valentine GIERCZAK

TITRE :

IMPACT DE QUATRE PROTOCOLES D'IMMUNOSUPPRESSION SUR
L'INCIDENCE DE LA THROMBOPÉNIE APRÈS TRANSPLANTATION RÉNALE

CONCLUSION :

L'objectif de notre étude était de comparer l'incidence de la thrombopénie dans la première semaine après transplantation rénale selon 4 schémas d'immunosuppression. Les patients inclus dans notre étude retrospective ont reçu un traitement d'induction par Thymoglobulin (THY) ou Grafalon (GRA) et un traitement d'entretien par Everolimus (EVR) ou Mycophenolate Mofetil (MMF), associé au Tacrolimus et aux corticostéroïdes. La thrombopénie était définie par un taux de plaquettes inférieur à 150 G/l. Sur les 237 patients inclus entre le 27 juillet 2016 et le 7 septembre 2018, 64.6% ont présenté une thrombopénie dans la première semaine après transplantation. L'incidence de la thrombopénie était plus élevée chez les patients sous GRA en comparaison à ceux sous THY ($p=0.004$). Le nadir de plaquettes et la valeur des plaquettes à la sortie d'hospitalisation étaient également plus bas chez les patients sous GRA (respectivement $p=0.002$ et $p=0.249$). La thrombopénie dans le groupe GRA-EVR était également plus fréquente et prononcée que dans les groupes THY-MMF, THY-EVR et GRA-MMF. L'induction par GRA était le seul facteur de risque de thrombopénie persistant en analyse multivariée ($p=0.002$). L'incidence d'hémorragies sévères, de transfusion de culots globulaires et de reprise chirurgicale étaient comparables dans les différents groupes, ainsi que les taux de reprise retardée de la fonction du greffon, de rejet, de perte du greffon et de décès avec un suivi moyen de 25 ± 8 mois. Au final, un schéma d'immunosuppression associant GRA et EVR semble être à l'origine d'une thrombopénie plus fréquente et sévère qu'il ne faut pas négliger, bien que celle-ci ne semble pas être responsable de plus de complications cliniques.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 3/4/2020

LE DOYEN



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