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Management of immunosuppression after kidney transplant failure: effect on patient sensitization.

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Abbreviations

CNI: calcineurin inhibitor

PRA: panel reactive antibody

DSA: donor specific antibody

EC: early cessation

HLA: human leukocyte antigen

IS: immunosuppression

KT: kidney transplant

KTF: kidney transplant failure

MFI: mean fluorescence intensity

MMF: mycophenolate mofetil

PT: prolonged treatment

T+: treatment period

T-: period after cessation of treatment

Introduction

The number of patients on kidney transplant (KT) waiting lists is continuously increasing. About 15% of these patients have already had a KT [1,2]. In many cases they develop human leucocyte antigen (HLA) sensitization during their first graft or during renal replacement therapy after reduction of immunosuppressive treatment [3], which makes access to a repeat KT more difficult. Longer waiting time is associated with lower patient survival [4–6] and with less likelihood of a repeat transplant [7]. It is necessary therefore to avoid the appearance of new HLA antibodies.

Documented information on the effect of maintaining immunosuppression (IS) after kidney transplant failure (KTF) is scarce. Retrospective studies suggest that maintenance decreases both the rate of allograft nephrectomy [8,9] and the development of HLA antibodies [10–13] thereby improving access to a second graft. However, maintenance immunosuppression is associated with higher rates of infection [9,14], cardiovascular events [15] and neoplasia [16]. First-year mortality in patients going back to dialysis after KT failure is greater than in those not having received a graft [17,18] mainly for cardiac or infectious reasons [19]. Hence, there are no current official guidelines for the management of immunosuppressive treatment after KTF [20]. In most instances, previous studies have suggested (i) stopping anti-metabolite treatments in the event of KTF, (ii) progressive reduction of CNI treatment followed by cessation within 1 month [21,22] or 3 months [23] and (iii) reduction of corticosteroids with delayed cessation followed by resumption of treatment on the occurrence of symptoms related to graft intolerance [24]. The British Transplantation Society suggests maintenance of immunosuppression when the living donor transplant is planned in the year following KTF [20].

The authors of a recent literature review suggested continuing CNI treatment at least as long as the allograft was viable but to stop it in the event of nephrectomy [25].

The aim of this study was to assess the effect of cessation or maintenance of immunosuppressive treatment on patient sensitization after a return to dialysis, and treatment tolerance so as to devise the best strategy for managing immunosuppressive drugs after KTF.

Patients and methods

Patients and data

This retrospective study was performed in three French KT centers (Gabriel Montpied Hospital, CHU Clermont-Ferrand; Bois-Guillaume Hospital, CHU Rouen; Bretonneau Hospital, CHRU Tours). Inclusion criteria were: (i) kidney transplant patients aged more than 18 years (ii) loss of graft function between June 2007 and June 2017 requiring renal replacement therapy (iii) investigation for HLA antibodies over at least 12 months after return to dialysis or development of a donor specific antibody (DSA) in the follow-up period, (iv) recorded dates of cessation of immunosuppressive treatments and (v) minimum follow-up of 12 months.

The medical and demographic characteristics of the patients were recovered from the CRISTAL prospective database and from patient medical files in the dialysis and transplantation centers taking part.

The following data were collected: (i) general patient characteristics: sex, date of birth, weight, height, blood group, type of dialysis before transplantation, initial kidney disease, (ii) information relating to the transplantation: date of the graft, number of previous transplants,

type and age of the donor, number of HLA mismatches, induction therapy, kidney rejection classification and treatment undertaken, transfusion, (iii) evolution after return to dialysis: date of loss of KTF, type of dialysis, immunosuppressive drugs being taken at time of KTF and date at when they were discontinued, infections requiring hospitalization, cardiovascular events such as cerebrovascular accidents, acute coronary syndrome, cardiac rhythm disorders, hospitalization for heart failure, symptomatic occlusive disease of the lower extremities (type and date of first episode), neoplasia (type and date of diagnosis), graft intolerance syndrome (date), allograft nephrectomy (date, indication and occurrence of complication), (iv) date of waiting list registration for retransplantation, patient status at last follow-up (v) date of any new graft.

Immunological data

Anti-HLA antibodies were detected by LUMINEX LabScreen Single Antigen assays, either One Lambda, Canoga Park, CA (Clermont-Ferrand and Tours) or Immucor Lifecodes, (Rouen). The two techniques are comparable [26].

The data collected were: (i) presence of antibodies before transplantation, DSA or not, (ii) presence of HLA class I and/or class II antibodies on KTF (mean fluorescence intensity [MFI] of the dominant DSA), (iii) development of de novo DSA, defined by MFI greater than or equal to 1000, (iv) panel reactive antibodies (PRA) provided by the French biomedical agency. Hypersensitized candidates to kidney transplantation were defined by an PRA ≥85%.

Definition of groups

Prolonged treatment (PT) with immunosuppressive drugs after KTF was defined as maintenance of therapy for at least 3 months after function loss. Patients who stopped

treatment during this period were assigned to the early cessation (EC) group. For the main analysis, only calcineurin inhibitors (CNI) were taken into consideration.

A complementary analysis to assess the rate of development of HLA antibodies with and without CNI treatment was performed after establishment of two study periods. Treatment period (T+) was the period from KTF to the date of cessation of immunosuppressive treatment, during which patients received IS. Those who stopped treatment during the first 3 months were excluded from analysis. Patients studied during the period from cessation of immunosuppressive treatment to performance of a new graft, death or last follow-up were assigned to the non-treatment (T-) period. Those in whom DSAs developed during the T+ period were excluded from the T- group.

Statistical analyses

Statistical analysis was performed using Stata software (version 13; StataCorp, College Station, Texas, USA). All tests were two-sided, with a Type I error set at 0.05. Categorical parameters were expressed as number of patients (associated percentages), and continuous data as mean ± standard deviation or as median [interquartile range], according to statistical distribution. The patients were divided into two groups according to the duration of anti-calcineurin treatment received after KTF (less than 3 months or greater than or equal to 3 months). Because there was no effect of the center (tested by mixed models), comparisons of these two independent groups were realized by statistical inference usual tests: categorical variables were compared using the chi-square test or the Fisher exact test; and quantitative data were compared between groups with the Student's t-test or the Mann-Whitney test, as appropriate. The Gaussian distribution was verified by the Shapiro-Wilk test and homoscedasticity by the Fisher-Snedecor test. The same analyses were performed to compare patients according to the duration of their corticosteroid treatment. When there were more than two groups to be compared (type of treatment: EC vs MMF vs ICN vs MMF+ICN),

quantitative data were compared between groups by ANOVA or Kruskal-Wallis test (normality verified by the Shapiro-Wilk test and homoscedasticity by the Bartlett's test). Categorical variables were compared as described previously, followed by the Marascuilo procedure if appropriate (omnibus p-value less than 0.05). For multivariate analysis, multiple logistic regression was used to study the development of DSA, considering the covariables according to the results of univariate analysis and their clinical relevance, notably for prolonged treatment with anti-calcineurin. The results were expressed as odds ratio (OR) and 95% confidence interval (95% CI). For secondary outcomes, other multivariate analyses, linear or logistic depending on the nature of the dependent variable, were performed according to the same principles. The development of DSA was also estimated using the Kaplan-Meier method, and the two groups (prolonged corticosteroid treatment and early cessation) were compared using the log-rank statistic. In addition, the patient sample was divided into two periods (T+ and T-), and events such as the development of de novo DSA, cardiovascular disorders and allograft nephrectomy were studied by mixed logistic regressions to take into account non-independence of the data (because a patient could be classified in both periods).

Institutional review board

This study was approved on 03 September 2019 by the ethical research committee ("Comité de Protection des Personnes Sud-Est 6") (IRB 00008526)

Results

General characteristics (Table 1)

A total of 119 patients with KTF were included in the study. Their general characteristics are given in Table 1. The patients were predominantly male (72.3%), aged

49.2 ± 14.5 years and had received a first KT (85.7%) whose median duration was 54 [9; 122] months. At the last KT follow-up, 68.9% had a DSA. The main cause of graft loss was rejection (60.5%). In the event of KTF, patients received triple IS comprising calcineurin inhibitors (95.0%), mycophenolate mofetil (MMF) (91.6%) and corticosteroids (91.6%). One hundred patients (84.0%) were on a waiting list for KT. Median follow-up time was 2.9 [1.6; 4.6] years.

Influence of prolonged treatment with calcineurin inhibitors (Tables 1 and 2)

There were no significant differences in general characteristics between the TP group (n=52, 43.7%) and the EC group (n=67, 56.3%) (Table 1).

During follow-up, de novo DSAs were observed in 30/52 (57.7%) patients in the TP group as against 52/67 (77.6%) in the EC group (p=0.02) (Figure 1). In multivariate analysis, adjusted for prolonged corticosteroid treatment, prolonged MMF treatment, graft loss by rejection, allograft nephrectomy and duration of graft function, prolonged treatment with CNI was always associated with a lower development of DSA (OR=0.39, 95% CI [0.16; 0.98] p=0.04) (Figure 2). The median levels of panel reactive antibody (PRA) class I and II (assessed in 99 patients) at first follow-up were similar in the two groups (Table 2), at last follow-up was higher in the EC group (97 [67; 99]) than in the PT group (41 [24; 96], p=0.002), as was the number of sensitized patients, who accounted for 38% in the EC group and 17% in the PT group (p=0.03). In multivariate analysis adjusted for prolonged corticosteroid treatment, prolonged MMF treatment, graft loss by rejection, allograft nephrectomy, transfusion, the presence of DSA at the time of KTF and duration of graft function, the number of patients with an PRA ≥85% was significantly lower in the PT group, OR=0.28, 95% CI [0.10; 0.78] p=0.02.

The rate of graft intolerance syndrome was 15.4% in the PT group as against 17.9% in the EC group (p=0.72). Allograft nephrectomy was observed in 19 (36.5%) PT patients and in 33 (49.3%) EC patients, p=0.17. PT and EC patients had similar rates of infections, cardiovascular events, neoplasia and deaths (Table 2). At 3 years, the rate of retransplantation was similar in the two groups : 36.1% [24.4; 51.2] in EC group, 39.9% [25.5; 58.5] in PT group p=0.73.

Analysis of periods with (T+) or without (T-) treatment with CNI (Table 3)

We excluded from the final analysis i) 34/86 patients in the T+ period because their treatment had been stopped in the first 3 months, ii) 18/108 patients in the T- period because a DSA had developed during the T+ period. Overall, patients were significantly less sensitized during the T+ period than during the T- period (34.6% and 70.0%, respectively, p=0.01). Of the 18 patients sensitized during the T+ period, 11 (61.1%) were still receiving corticosteroid treatment at 3 months and 13 (72.2%) had stopped MMF.

Cardiovascular and neoplastic events and deaths occurred with the same frequency during the two periods studied. The allograft nephrectomy rate was also comparable, 15 (28.8%) during the T+ period, and 24 (26.7%) during the T- period, p=0.78.

Effect of corticosteroid and/or MMF treatment after KTF (Tables 4 and 5)

Corticosteroid treatment was maintained for more than 3 months (prolonged treatment) in 69/119 patients (58.0%). However, the rate of development of DSA in this group was similar to that in the EC group, respectively 47/69 (68.1%) and 35/50 (70.0%), p=0.83. The PRA at last follow-up and the rate of allograft nephrectomy were the same in the two groups of patients (Table 4). However, the rate of infections was significantly higher in

patients with prolonged corticosteroid treatment (39.1%) than in those in the EC group (20.0%), p=0.03. Multivariate analysis adjusted for age, prolonged CNI treatment, prolonged MMF treatment, graft loss by rejection and graft duration confirmed that prolonged corticosteroid treatment is associated with a greater risk of infection, OR=2.66, 95% CI [1.09; 6.46], p=0.03.

Combined MMF and CNI treatment was observed in 23/52 patients receiving PT and in 9 patients without CNI treatment at 3 months. Development of DSA was similar in patients on combined therapy than in those receiving CNI treatment alone (52.2% vs 62.1% respectively, p=0.92) and there was also no difference of PRA between these two groups (69 [23; 97] vs 77 [32; 95] respectively, p=1.00). A lower rate of hypersensitized patients was observed in combined therapy (n=6, 35.3%) than in CNI monotherapy (n=11, 45.8%) and without immunosuppressive treatment (n=30, 60%), p=0.04. The rate of infections was also higher with MMF + CNI treatment (52.2%) than with CNI alone (24.1%), p=0.21 (Table 5).

Discussion

We report the first multicenter retrospective study to compare the effects of prolonged CNI immunosuppression following KTF on patient sensitization. Our results show that prolonged CNI treatment is associated with lower levels of *de novo* DSA and patient hypersensitization at the last follow-up. Several studies have also shown lower sensitization in patients continuing immunosuppressive treatment after LGF. In a retrospective American series involving 49 KT patients with graft failure, anti-HLA sensitization was lower when immunosuppressive treatment (either CNI or MMF) was maintained for more than 3 months than in the event of early cessation: OR=5.78, 95% CI [1.37; 24.44] [12]. A single-center

retrospective study performed in the USA compared the rate of hypersensitized patients at last follow-up, defined as such by a PRA >80%, in 119 recipients of a kidney or kidney-pancreas transplant following KTF. The rate of hypersensitized patients was 8% (n=2/24) when immunosuppression was maintained and 68% (n=65/95) if it was stopped (p<0.001) [10]. A recent English study of 41 patients confirmed that a reduction of IS after KTF followed by cessation resulted in the development of DSAs and in all the patients becoming sensitized whether they had undergone nephrectomy or not [11].

Our results showed that the development of de novo DSA after KTF was greater when anti-calcineurin treatment was stopped during the first 3 months than when it was maintained. They also showed that DSAs recurred mainly (in 70% of cases) after cessation of treatment, including for patients continuing treatment at least 3 months after KTF. The results are similar to those reported in a retrospective Spanish series involving 76 patients in which the authors observed that DSAs developed in 78.4% of patients after cessation of IS [27].

In our study, maintenance or cessation of prolonged CNI treatment was not associated with an increased rate of infections, cancers, cardiovascular complications or deaths. These results are consistent with those in previously reported case series. For example, in a study performed in the USA of 102 KT patients with KTF receiving or not immunosuppressive therapy of more than 3 months' duration the authors recorded similar rates of cancer (n=0 and n=4, respectively), death from infection (4% and 23%, respectively) and death from all causes (22% and 44%, respectively) [12]. In contrast, another study recently performed in the USA involving 186 patients with KTF, the infection rate was significantly higher in the group continuing to receive IS (88%) than in the group where IS was discontinued (38%), p<0.001

[14]. However, the authors did not specify which type of immunosuppressive treatment was used.

Prolonged corticosteroid therapy is the most commonly implemented regimen [20,21,28,29] but we did not observe its effect on i) the development of DSAs, (ii) PRA, (iii) the incidence of graft intolerance syndrome and (iv) allograft nephrectomy rate. In contrast, multivariate analysis showed an increased likelihood of infection with prolonged corticosteroid treatment. Another retrospective multicenter series showed simular results [30]. The authors reported an increase in infectious complications (OR=3.4, 95% CI [2.5; 4.5] p<0.001), cardiovascular complications (OR=3.0, 95% CI [1.1; 8.0] p=0.02) and deaths (OR=3.4, 95% CI [1.8; 6.3] p<0.001) in patients receiving IS treatment after KTF mainly corticosteroids (98%) [30].

Our study has certain limitations. First, because it was retrospective and performed in three different centers, the management of IS was not uniform. In the absence of guidelines for the management of immunosuppressive treatment after KTF [20], current treatment protocols differ between KT centers (appendix Table) and the decision to reduce immunosuppressive therapy is often left to the discretion of the nephrologist in the dialysis center [20]. Our study suggests maintenance of CNI immunosuppression until a new transplant is performed, irrespective of any intervening transplantectomy, so as to reduce the sensitization level, time on the waiting list [2,31]. We didn't observe any difference of length of time on the waiting list between patients with early cessation or prolonged CNI treatment. Indeed French biomedical agency give a priority access to renal transplantation for patients with PRA >85%. That allowed to reduce their waiting time. Second, in these studies, as in ours, the dose or target level of CNI during maintenance treatment was not specified [13]. Only in a recent study was the development of HLA antibodies assessed according to levels of

tacrolimus. This study showed a cut-off residual level of tacrolimus of 3ng/ml, below which patients had a higher cPRA at M24 (89 [70; 99] vs 0 [0; 43], p<0.001).[30]

In conclusion, our findings show that maintenance of long term CNI therapy limits patient sensitization after KTF without increasing the rates of infections or cardiovascular events. The dose and target rates of CNI treatment remain to be determined and our results should be validated by a prospective randomized study.

References

1. Hiesse C. Épidémiologie de la transplantation rénale en France. *Néphrologie Thérapeutique*. 2013;9(6):441-450. doi:10.1016/j.nephro.2013.02.002

2. UNOS, annual report 2016. https://unos.org

3. Scornik JC, Kriesche H-UM. Human leukocyte antigen sensitization after transplant loss: timing of antibody detection and implications for prevention. *Hum Immunol*. 2011;72(5):398-401. doi:10.1016/j.humimm.2011.02.018

4. Ojo AO, Wolfe RA, Agodoa LY, et al. Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation: Multivariate Analyses from the United States Renal Data System1,2. *Transplantation*. 1998;66(12):1651-1659. doi:10.1097/00007890-199812270-00014

5. Redfield RR, Gupta M, Rodriguez E, Wood A, Abt PL, Levine MH. Graft and patient survival outcomes of a third kidney transplant. *Transplantation*. 2015;99(2):416-423. doi:10.1097/TP.0000000000000332

6. Meier-Kriesche H-U, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation*. 2002;74(10):1377-1381. doi:10.1097/00007890-200211270-00005

7. Wong G, Chua S, Chadban SJ, et al. Waiting Time Between Failure of First Graft and Second Kidney Transplant and Graft and Patient Survival. *Transplantation*. 2016;100(8):1767-1775. doi:10.1097/TP.0000000000000953

8. Del Bello A, Congy-Jolivet N, Sallusto F, et al. Donor-specific antibodies after ceasing immunosuppressive therapy, with or without an allograft nephrectomy. *Clin J Am Soc Nephrol CJASN*. 2012;7(8):1310-1319. doi:10.2215/CJN.00260112

9. Woodside KJ, Schirm ZW, Noon KA, et al. Fever, infection, and rejection after kidney transplant failure. *Transplantation*. 2014;97(6):648-653. doi:10.1097/01.TP.0000437558.75574.9c

10. Augustine JJ, Woodside KJ, Padiyar A, Sanchez EQ, Hricik DE, Schulak JA. Independent of nephrectomy, weaning immunosuppression leads to late sensitization after kidney transplant failure. *Transplantation*. 2012;94(7):738-743. doi:10.1097/TP.0b013e3182612921

11. Nimmo AMSA, McIntyre S, Turner DM, Henderson LK, Battle RK. The Impact of Withdrawal of Maintenance Immunosuppression and Graft Nephrectomy on HLA Sensitization and Calculated Chance of Future Transplant. *Transplant Direct*. 2018;4(12):e409. doi:10.1097/TXD.0000000000000848

12. Casey MJ, Wen X, Kayler LK, Aiyer R, Scornik JC, Meier-Kriesche H-U. Prolonged immunosuppression preserves nonsensitization status after kidney transplant failure. *Transplantation*. 2014;98(3):306-311. doi:10.1097/TP.0000000000000057

13. López del Moral Cuesta C, Guiral Foz S, Gómez Pereda D, et al. Immunosuppression with Calcineurin Inhibitor after Renal Transplant Failure Inhibits Allosensitization. *Biomedicines*. 2020;8(4):72. doi:10.3390/biomedicines8040072

14. Gregoor PJ, Kramer P, Weimar W, van Saase JL. Infections after renal allograft failure in patients with or without low-dose maintenance immunosuppression. *Transplantation*. 1997;63(10):1528-1530. doi:10.1097/00007890-199705270-00028

15. Meier-Kriesche H-U, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2004;4(10):1662-1668. doi:10.1111/j.1600-6143.2004.00573.x

16. van Leeuwen MT, Webster AC, McCredie MRE, et al. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. *BMJ*. 2010;340:c570. doi:10.1136/bmj.c570

17. Kaplan B, Meier-Kriesche H-U. Death after graft loss: an important late study endpoint in kidney transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2002;2(10):970-974. doi:10.1034/j.1600-6143.2002.21015.x

18. Aniort J, Kaysi S, Garrouste C, et al. CKD complications in kidney-transplanted patients going back to dialysis: impact on patients outcomes. *J Nephrol*. 2018;31(1):147-155. doi:10.1007/s40620-017-0449-z

19. Gill JS, Abichandani R, Kausz AT, Pereira BJG. Mortality after kidney transplant failure: the impact of non-immunologic factors. *Kidney Int*. 2002;62(5):1875-1883. doi:10.1046/j.1523-1755.2002.00640.x

20. Andrews PA, Standards Committee of the British Transplantation Society. Summary of the British Transplantation Society Guidelines for Management of the Failing Kidney Transplant. *Transplantation*. 2014;98(11):1130-1133. doi:10.1097/TP.0000000000000426

21. Pham P-T, Pham P-C. Immunosuppressive management of dialysis patients with recently failed transplants. *Semin Dial*. 2011;24(3):307-313. doi:10.1111/j.1525-139X.2011.00864.x

22. Marinaki S, Skalioti C, Boletis J. Patients After Kidney Allograft Failure: Immunologic and Nonimmunologic Considerations. *Transplant Proc*. 2015;47(9):2677-2682. doi:10.1016/j.transproceed.2015.09.054

23. Morales A, Gavela E, Kanter J, et al. Treatment of renal transplant failure. *Transplant Proc*. 2008;40(9):2909-2911. doi:10.1016/j.transproceed.2008.09.047

24. Coppolino G, Criseo M, Nostro L, et al. Management of patients after renal graft loss: an open question for nephrologists. *Ren Fail*. 2006;28(3):203-210. doi:10.1080/08860220600580357

25. Bunthof KLW, Hazzan M, Hilbrands LB. Review: Management of patients with kidney allograft failure. *Transplant Rev Orlando Fla*. 2018;32(3):178-186. doi:10.1016/j.trre.2018.03.001

26. Bertrand D, Farce F, Laurent C, et al. Comparison of Two Luminex Single-antigen Bead Flow Cytometry Assays for Detection of Donor-specific Antibodies After Renal Transplantation. *Transplantation*. 2019;103(3):597-603. doi:10.1097/TP.0000000000002351

27. García Montemayor V, Agüera ML, Rabasco C, Navarro MD, Rodríguez Benot A, Aljama P. Development of Donor-Specific Anti-HLA Antibodies After Restarting Hemodialysis Due to Graft Failure. *Transplant Proc*. 2015;47(9):2626-2630. doi:10.1016/j.transproceed.2015.10.018

28. Kendrick EA, Davis CL. Managing the failing allograft. *Semin Dial*. 2005;18(6):529-539. doi:10.1111/j.1525-139X.2005.00100.x

29. Smak Gregoor PJ, Zietse R, van Saase JL, et al. Immunosuppression should be stopped in patients with renal allograft failure. *Clin Transplant*. 2001;15(6):397-401. doi:10.1034/j.1399-0012.2001.150606.x

30. Lucisano G, Brookes P, Santos-Nunez E, et al. Allosensitization after transplant failure: the role of graft nephrectomy and immunosuppression - a retrospective study. *Transpl Int Off J Eur Soc Organ Transplant*. 2019;32(9):949-959. doi:10.1111/tri.13442

31. Réseau épidemiologie et information en néphrologie (REIN), rapport annuel de 2016. https://www.agence-biomedecine.fr/IMG/pdf/rapportrein2016.compressed.pdf

Table 1 - Characteristics of prolonged immunosuppressive treatment or early cessation (before month 3) after kidney transplant failure .

Table 2 - Outcomes of prolonged immunosuppressive treatment or early cessation (before month 3) after kidney transplant failure.

Table 3 - Outcomes under calcineurin inhibitors treatment (period T+) and weaned off calcineurin inhibitors treatment (period T-).

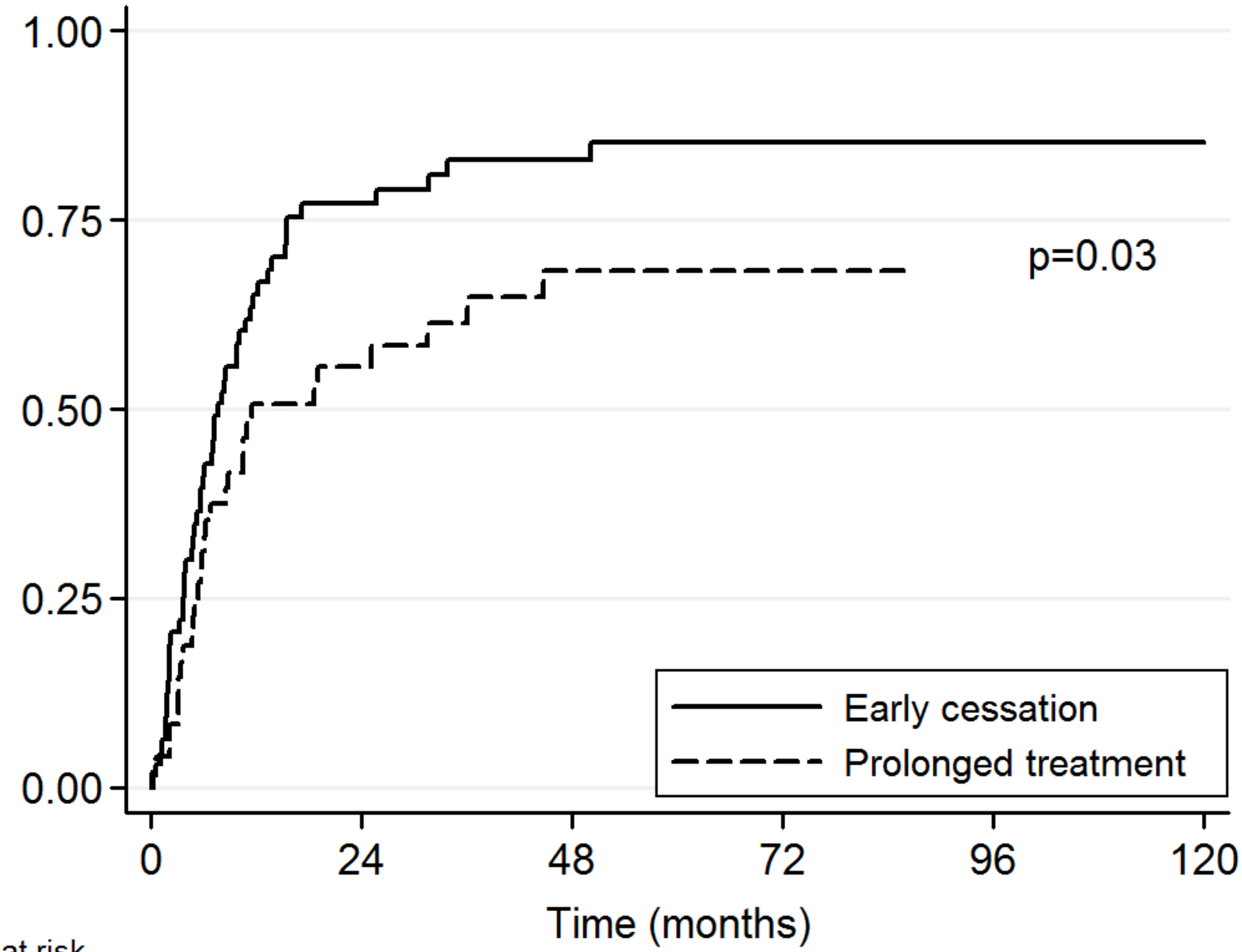
Table 4 - Outcomes of prolonged corticosteroid treatment or early cessation (before month 3) after kidney transplant failure.

Table 5 - Outcomes of prolonged CNI and MMF traitement or early cessation after kidney transplant failure.

Table 6 - Management of immunosuppression in 11 adult transplant centers of the Spiesser group

Figure 1- Development of de novo DSAs according to prolonged CNI treatment (after month 3) or early cessation.

Figure 2 - Multivariate analysis of predictive factors of development of de novo DSAs after loss of graft function



Number at risk						
Early cessation	63	13	8	5	2	2
Prolonged treatment	48	16	8	2	0	0

	OR	95% CI	p-value
Prolonged treatment	0.39	[0.16 ; 0.98]	0.044
Corticosteroid > 3 months	1.19	[0.51 ; 2.79]	0.684
MMF > 3 months	0.83	[0.33 ; 2.10]	0.687
Graf failure by rejection	1.08	[0.37 ; 3.13]	0.888
Allograft nephrectomy	0.39	[0.14 ; 1.06]	0.066
Duration of allograft survival	0.83	[0.62 ; 1.11]	0.202

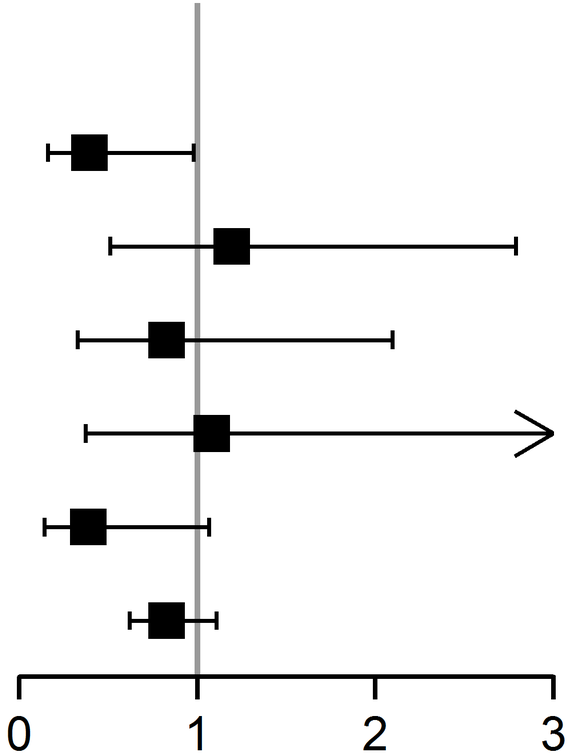


Table 1 - Characteristics of prolonged immunosuppressive treatment or early cessation (before month 3) after kidney transplant failure .

	Total n=119	**Prolonged treatment n=52**	**Early cessation n=67**	**p-value**
Male sex	86 (72.3)	36 (69.2)	50 (74.6)	0.51
Age (years)	49.2 ± 14.5	48.9 ± 14.9	49.4 ± 14.3	0.87
BMI (kg/m^2)	24.6 ± 5.4	24.4 ± 5.2	24.6 ± 5.7	0.84
Blood group				
O	50 (42.0)	26 (50.0)	24 (35.8)	
B	10 (8.4)	4 (7.7)	6 (9.0)	0.21
A	55 (46.2)	22 (42.3)	33 (49.3)	
AB	4 (3.4)	0 (0.0)	4 (6.0)	
First kidney transplantation	102 (85.7)	43 (82.7)	59 (88.1)	0.41
Live donor	10 (8.7)	6 (12.0)	4 (6.2)	0.33
Induction treatment	106/109 (97.2)	46/47 (97.9)	60/62 (96.8)	1.00
Thymoglobulin	41/106 (38.7)	20/46 (43.5)	21/60 (35.0)	0.37
Cause of graft loss				
Rejection	72 (60.5)	29 (55.8)	43 (64.2)	
Kidney disease recurrence	7 (5.9)	6 (11.5)	1 (1.5)	0.16
Vascular	21 (17.6)	9 (17.3)	12 (17.9)	
Other	19 (16.0)	8 (15.4)	11 (16.4)	
Transfusion during graft	79 (66.4)	32 (61.5)	47 (70.1)	0.32
Acute rejection	68 (57.1)	29 (55.8)	39 (58.2)	0.79
Humoral	31/67 (46.3)	14/29 (48.3)	17/38 (44.7)	0.77
Maintenance immunosuppressive regimen at KTF				
Tacrolimus	82 (68.9)	34 (65.4)	48 (71.6)	0.47
Ciclosporin	31 (26.1)	18 (34.6)	13 (19.4)	0.06
Mycophenolate mofetil	109 (91.6)	49 (94.2)	60 (89.6)	0.51
mTOR inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	NA
Corticosteroids	109 (91.6)	46 (88.5)	63 (94.0)	0.33
Presence of anti-HLA d0 graft	21/118 (17.8)	7 (13.5)	14/66 (21.2)	0.27
Presence of DSA on LGF	69/118 (58.5)	32 (61.5)	37/66 (56.1)	0.55
PRA (n=99)	0 [0; 65.3]	0 [0; 52.7]	0 [0; 76.7]	0.54
PRA ≥85% on LGF	16/99 (16.2)	3/40 (7.5)	13/59 (22.0)	0.05

Abbreviations: BMI, body mass index; DSA, donor specific antibody; HLA, human leukocyte antigen; KTF, kidney transplant failure; LGF, loss of graft function; NA, not applicable; PRA, panel reactive antigen.

The data are expressed as number of patients (associated percentage), mean ± standard deviation, or median [interquartile range].

Table 2 - Outcomes of prolonged immunosuppressive treatment or early cessation (before month 3) after kidney transplant failure.

	Total n=119	**Prolonged treatment n=52**	**Early cessation n=67**	**p-value**
Development of DSA	82 (68.9)	30 (57.7)	52 (77.6)	0.02
Class 1	39/82 (47.6)	11/30 (36.7)	28/52 (53.9)	
Class 2	21/82 (25.6)	10/30 (33.3)	11/52 (21.2)	0.29
Classes 1 and 2	22/82 (26.8)	9/30 (30.0)	13/52 (25.0)	
PRA last FU (n=100)	88.5 [53.5; 99]	71 [24; 96]	97 [67; 99]	0.002
PRA ≥ 85%	55/100 (55.0)	17/41 (41.5)	38/59 (64.4)	0.03
Transplantectomy	52 (43.7)	19 (36.5)	33 (49.3)	0.17
Graft intolerance syndrome	20 (16.8)	8 (15.4)	12 (17.9)	0.72
Booked on waiting list	100 (84.0)	41 (78.8)	59 (88.1)	0.17
New graft	53/100 (53.0)	21/41 (51.2)	32/59 (54.2)	0.77
Retransplant waiting time (years) (n=53)	2.4 [1.5; 4.0]	2.5 [1.5; 3.2]	2.4 [1.4; 4.3]	0.45
Transfusion after LGF	63 (52.9)	27 (51.9)	36 (53.7)	0.85
Patients on corticosteroids at M3	69 (58.0)	35 (67.3)	34 (50.7)	0.07
Infection	37 (31.1)	19 (36.5)	18 (26.9)	0.26
Cancer	11 (9.2)	7 (13.5)	4 (6.0)	0.21
Cardiovascular event	24/118 (20.3)	9/51 (17.6)	15 (22.4)	0.53
Deaths	6/105 (5.7)	4/49 (8.2)	2/56 (3.6)	0.41

Abbreviations: CNI, calcineurin inhibitors; DSA, donor specific antibody; FU, follow up; LGF, loss of graft function, PRA, panel reactive antigen.

The data are expressed as number of patients (associated percentage), or median [interquartile range].

Table 3 - Outcomes under calcineurin inhibitors treatment (period T+) and weaned off calcineurin inhibitors treatment (period T-).

	Period T+ n=52	**Period T- n=90**	**p-value**
Development of DSA	18 (34.6)	63 (70.0)	0.01
Transplantectomy	15 (28.8)	24 (26.7)	0.78
Cancer	4 (7.7)	5 (5.6)	0.62
Cardiovascular event	5 (9.6)	15 (16.7)	0.25
Deaths	0 (0.0)	5 (5.6)	NE

Abbreviations: CNI, calcineurin inhibitors; DSA, donor specific antibody; NE, not estimated.

Treatment period (T+) was the period from KTF to the date of cessation of immunosuppressive treatment, during which patients received IS. Those who stopped treatment during the first 3 months were excluded from analysis. Patients studied during the period from cessation of immunosuppressive treatment to performance of a new graft, death or last follow-up were assigned to the non-treatment (T-) period. Those in whom DSAs developed during the T+ period were excluded from the T- group.

The data are expressed as number of patients (associated percentage).

Table 4 - Outcomes of prolonged corticosteroid treatment or early cessation (before month 3) after kidney transplant failure.

	Prolonged corticosteroid treatment n=69	**Early corticosteroid cessation n=50**	**p-value**
Development of DSA	47 (68.1)	35 (70.0)	0.83
PRA last FU (n=100)	86 [51; 98]	90 [59; 99]	0.56
PRA ≥85%	34/61 (55.7)	21/39 (53.8)	0.85
Transplantectomy	29 (42.0)	23 (46.0)	0.67
Infection	27 (39.1)	10 (20.0)	0.03
Cancer	6 (8.7)	5 (10.0)	1.00
Cardiovascular event	14 (20.3)	10 (20.4)	0.99
Deaths	3/63 (4.8)	3/42 (7.1)	0.68

Abbreviations: DSA, donor specific antibody; PRA, panel reactive antigen.

The data are expressed as number of patients (associated percentage) or median [interquartile range].

Table 5 - Outcomes of prolonged CNI and MMF traitement or early cessation after kidney transplant failure.

	Early cessation n=58	**MMF n=9**	**CNI n=29**	**MMF + CNI n=23**	**p-value**
Development of DSA	45 (77.6)	7 (77.8)	18 (62.1)	12 (52.2)	0.11
Transplantectomy	27 (46.6)	6 (66.7)	9 (31.0)	10 (43.5)	0.27
PRA on LGF (n=100)	0 [0;65]	87 [0; 99]	0 [0; 55]	0 [0; 48]	0.24
PRA last FU (n=100)	96 [61; 99]	97 [90; 99]	77 [32; 95]	69 [23; 97]	0.02
PRA ≥85%	30 (60.0)	8 (88.9)	11 (45.8)	6 (35.3)	0.04
Delta PRA	46 [0;99]	5.6[-1-86]	23 [0; 82]	24 [10; 65]	0.39
Corticosteroids at M3	28 (48.3)	6 (66.7)	22 (75.9)	13 (56.5)	0.09
Infections	16 (27.6)	2 (22.2)	7 (24.1)	12 (52.2)	0.13
Cancer	3 (5.2)	1 (11.1)	6 (20.7)	1 (4.3)	0.10
Cardiovascular event	13 (22.4)	2 (22.2)	4 (14.3)	5 (21.7)	0.83
Deaths	2/47 (4.3)	0 (0.0)	2/28 (7.1)	2/21(9.5)	0.80

Abbreviations: CNI, calcineurin inhibitors; DSA, donor specific antibody; LGF, loss of graft function; MMF, mycophnolate mofetil ; PRA, panel reactive antigen.

Delta PRA= PRA last FU – PRA on LGF

The data are expressed as number of patients (associated percentage), or median [interquartile range].

Table 6 - Management of immunosuppression in 11 adult transplant centers of the Spiesser group

Adult kidney transplant center	CNI	MMF	Corticosteroids	
Center 1	Reduction over several weeks	Cessation on LGF	NP	
Center 2	Reduction over several weeks	Cessation on LGF	NP	Only if graft project
Center 3	Tapering of treatment	Cessation on LGF	NP	Adapted to each cases
Center 4	Tapering of treatment	Cessation on LGF	NP	NP
Center 5	Tapering over3 months	Cessation on LGF	NP	Protocol
Center 6	Reduction over several weeks	Cessation on LGF	NP	
Center 7	Tapering	Maintenance if reinstated on the waiting list	Tapering	Protocol + case by case
Center 8	Tapering	Cessation on LGF	NP	
Center 9	Tapering	Cessation on LGF	NP	
Center 10	Tapering	NP	NP	
Center 11	Maintenance if reinstated on the waiting list otherwise immediate cessation	Maintenance if reinstated on the waiting list otherwise cessation at M1	NP	

Abbreviations: CNI, calcineurin inhibitors; LGF, loss of graft function; MMF, mycophenolate mofetil; NP, no protocol.

Figure 1- Development of de novo DSAs according to prolonged CNI treatment (after month 3) or early cessation.

Abbreviations: CNI, calcineurin inhibitor; DSA, donor specific antibody.

Figure 2 - Multivariate analysis of predictive factors of development of de novo DSAs after loss of graft function

Abbreviations: CI, confidence interval; CNI calcineurin inhibitors; DSA, donor specific antibody; LGF, loss of graft function; MMF, mycophenolate mofetil; OR; odds ratio.
In this analysis, duration of allograft survival is log-transformed.