Impact of G-CSF Therapy on Leukopenia and Acute Rejection Following Kidney Transplantation

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ABSTRACT

Background: Leukopenia is a common problem after kidney transplantation. The therapeutic approach typically includes a reduction of the immunosuppressive therapy, which is associated with an increased risk of rejection and allograft loss. Granulocyte colony-stimulating factor (G-CSF) is used as a therapeutic option to raise the leukocyte blood count; however, the effect on acute rejections is controversial.

Objective: The goal of this study is to examine the incidence of acute rejections following G-CSF therapy.

Methods: We retrospectively evaluated patients with leukopenia following kidney transplantation and G-CSF therapy between January 2007 and December 2017 at our center compared to controls with matched minimal leucocyte blood count in a matched pair analysis.

Results: We identified 12 patients, who received G-CSF therapy with a cumulative dose of 10.74 µg/kg body weight over a time frame of 4.3 days. G-CSF therapy resulted in a significantly shorter time period with leucocytes <3,000/µL (9.5 vs. 16.6 days), but also trended towards an increased risk of rejection within the next 30 days with three patients in the G-CSF group and no patient in the control group (p=0.06) developing an acute biopsy-proven rejection. Infection and mortality rate in the subsequent year were not different between groups.

Conclusion: G-CSF therapy decreases the duration of leukopenia post-kidney transplantation, but may also increase the risk of an acute rejection.

KEYWORDS: Kidney transplantation; Leukopenia; Granulocyte colony-stimulating factor; Rejection

INTRODUCTION

Leukopenia is a frequent complication following kidney transplantation, which typically occurs within the first year after transplantation. Up to 60% of patients develop at least one episode of leukopenia [1]. It is primarily related to the medication, such as lymphocyte-depleting agents like rabbit antithymocyte globulin (rATG), antimetabolic agents like azathioprine or mycophenolic acid (MPA), calcineurin inhibitors (CNIs), antiviral agents like ganciclovir or valganciclovir, and trimethoprim-sulfamethoxazole [2]. Viral infections have myelosuppressive effects and can cause leukopenia, i.e. infections with cytomegalovirus (CMV), parvovirus B19, human herpesvirus 6, and influenza [3].

Following leukopenia, patients exhibit an increased incidence of bacterial and CMV infections [4]. Since infection is the second most common cause of death after transplantation, leukopenia is a major risk factor for mortality [5]. It is also associated with an increased risk of allograft loss. The management of leukopenia typically includes a dose reduction or discontinuation of the potential causative medication, such as MPA or valganciclovir. However, a reduction of the maintenance immunosuppression is associated with an increased risk

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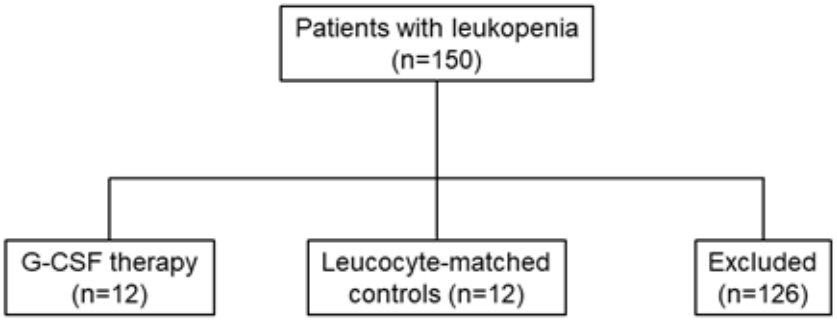

Figure 1: Flowchart of patient recruitment.

of allograft rejection, and stopping the anti-infective prophylaxis increases the risk of opportunistic infections [6]. Stimulation with recombinant granulocyte colony-stimulating factor (G-CSF) is a therapeutic strategy in drug-induced leukopenia and is often used as a prophylaxis in cancer patients receiving chemotherapy [7]. Small observational studies suggest that G-CSF might be a safe and effective approach to raise neutrophil blood count [8-12]. Similarly, G-CSF is used to treat leukopenia following solid organ transplantations including liver [13] and heart [14]. However, other studies suggest that G-CSF also increases the risk of acute rejections as described for liver [15] and heart transplant recipients [16] and also the risk of chronic allograft dysfunction in lung transplant recipients [17].

Importantly, the long-term effects of G-CSF therapy following kidney transplantation remain to be investigated. We therefore sought to determine the risk of rejection following G-CSF therapy within a follow-up time period of one year in a matched-pair analysis.

MATERIALS AND METHODS

Study Design

A retrospective analysis of 150 kidney transplant recipients with at least one episode of leukopenia between January 2007 and December 2017 at the Freiburg Transplant Center, Germany, was performed. Inclusion criteria were kidney transplantation or combined kidney and pancreas transplantation, leukopenia and G-CSF therapy. Leukopenia was defined as a leukocyte blood count <4,000/µL. The primary objective was to determine the impact of G-CSF therapy on the incidence of biopsy-proven kidney allograft rejection. We evaluated the following secondary outcomes: acute transplant failure, serum creatinine value one year after the episode of leukopenia, viral and bacterial infections within one year following leukopenia and mortality.

We identified 12 patients with an episode of leukopenia receiving G-CSF therapy within the defined time frame (Fig 1). As leukopenia was more severe in patients who received G-CSF therapy a matched pair analysis was performed. Matched pairs were identified by 1:1 matching for the minimal leukocyte blood count with a match tolerance of ≤200 leukocytes/µL. G-CSF was administered as filgrastim (Neupogen®, Amgen, Thousand Oaks, CA, USA). Clinical data were collected from historical records.

Statistical Analysis

All tests were 2-tailed; a p-value <0.05 was considered statistically significant. SPSS Statistics 25® software (IBM Corp., Armonk, NY) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation. Chi-square tests were performed on categorical variables. Student's t-tests were performed to determine the impact of categorical variables on continuous variables. Survival analysis was performed using the Kaplan-Meier method. Statistical dif

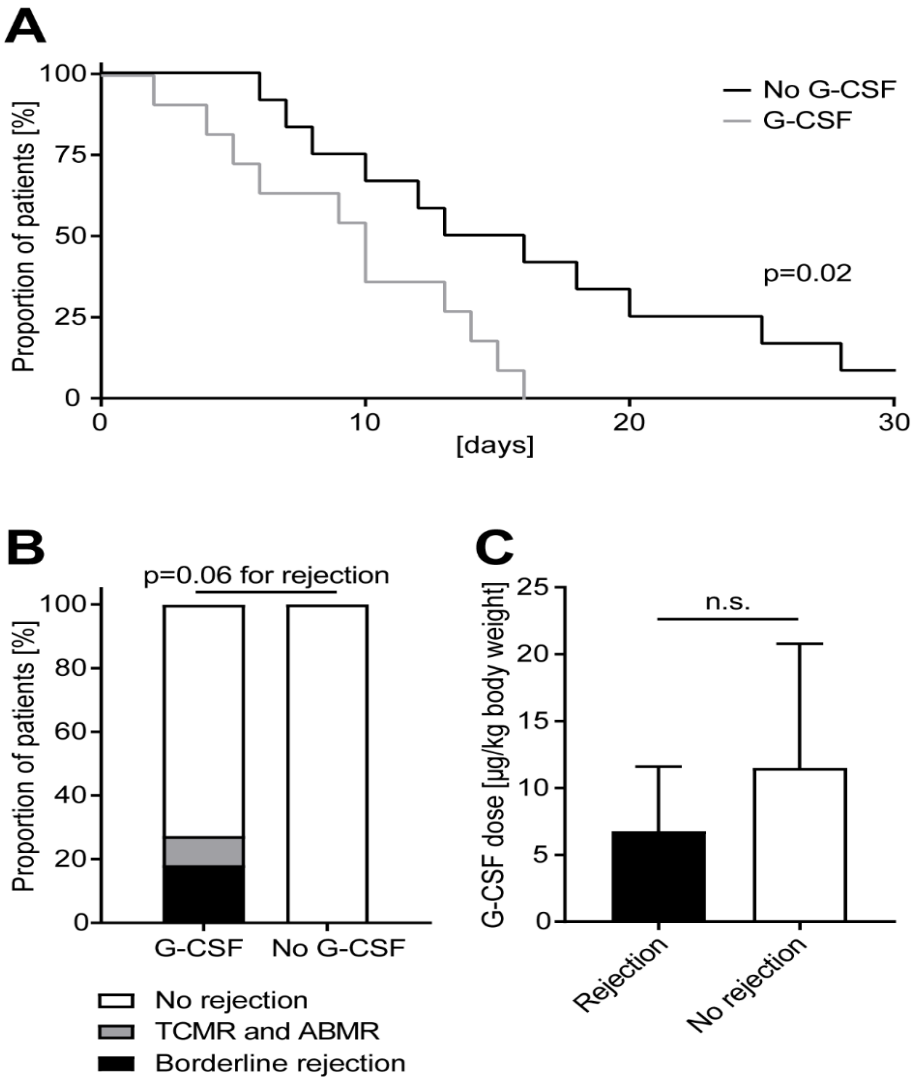

Figure 2: G-CSF therapy decreases the duration of leukopenia and trends to increase the risk of acute rejection independent of the total dose administered. Impact of G-CSF therapy on (A) the duration of leukopenia with a leukocyte count <3,000/µL, (B) on the incidence of acute rejections within the following 30 days, and (C) Impact of the cumulative G-CSF dose on the risk of rejection.

ferences were assessed using the log-rank test.

The study was approved by the ethics committee of the Freiburg Medical Center, Germany (protocol number 156/18).

RESULTS

We identified 12 patients with G-CSF therapy and compared them to 12 matched patients without G-CSF and a similar minimal leucocyte blood count (G-CSF group: 838.3/µL ± 331.7/µL, control group: 924.2/µL ± 311.2/µL, p=0.52, Fig 1 and Table 1). Leukopenia was observed after an average (SD) of 19.8 ± 41.3 weeks post-transplantation in the G-CSF treated group and after 33.6 ± 82.4 weeks in the control group (p=0.61, Table 1). The groups did not differ in baseline characteristics (Table 1). In the G-CSF group three patients received a living donation with two patients receiving a donation from their spouse and one patient receiving a donation from a first-degree relative. Two of the living donations were blood group incompatible (Table 1). In the control group four patients received

Table 1: Patient baseline characteristics.

Variables	G-CSF (n=12)	No G-CSF (n=12)	p-value
Minimal leucocyte count (/µL), mean ± SD	838.3 ± 331.7	924.2 ± 311.2	0.52
Minimal neutrophil count (n=8/8) (/µL), mean ± SD	372.5 ± 298.3	497.5 ± 206.3	0.35
Minimal lymphocyte count (n=8/6) (/µL), mean ± SD	410.0 ± 154.1	283.8 ± 192.1	0.21
Time of leukopenia following transplantation (weeks), mean ± SD	19.8 ± 41.3	33.6 ± 82.4	0.61
Female gender, n (%)	4 (0.33)	5 (0.4)	0.18
Recipient age (years), mean ± SD	50 ± 15.3	51.9 ± 13.0	0.74
Body weight (kg), mean ± SD	71.1 ± 9.1	66.6 ± 15.1	0.39
Body mass index (BMI) (kg/m2), mean ± SD	24.5 ± 2.4	23.2 ± 5.2	0.44
Time on dialysis (months), mean ± SD	53.8 ± 50.9	63.7 ± 55.9	0.67
Cold ischemia time (minutes) (n=6/8), mean ± SD	474.9 ± 343.3	342.0 ± 358.8	0.50
HLA mismatch (n=5/7), mean ± SD	2.7 ± 1.9	3.2 ± 0.8	0.61
Current PRA (n=8/9), mean ± SD	2.2 ± 6.7	20.4 ± 31.7	0.11
Highest PRA (n=8/9), mean ± SD	14.3 ± 25.6	30.1 ± 40.1	0.34
Renal disease, n (%)			
Genetic, n (%)	6 (0.5)	4 (0.33)	0.41
Autoimmune, n (%)	4 (0.33)	4 (0.33)	1.00
Postrenal, n (%)	1 (0.08)	1 (0.08)	1.00
Unknown, n (%)	1 (0.08)	3 (0.25)	0.27
Immunosuppressive therapy before transplantation, n (%)	6 (0.5)	6 (0.5)	1.00
Type of transplant			
Deceased donor, n (%)	9 (0.75)	8 (0.67)	0.65
Living donation, blood group compatible (ABOc), n (%)	1 (0.08)	3 (0.25)	0.27
Living donation, blood group incompatible (ABOi), n (%)	2 (0.17)	1 (0.08)	0.54
Previous kidney transplants, n (%)			
None, n (%)	8 (0.67)	9 (0.75)	0.65
1, n (%)	3 (0.25)	2 (0.17)	0.62
≥ 2, n (%)	1 (0.08)	1 (0.08)	1.00
CMV serostatus, n (%) (n=11/11)*			
D-/R-, n (%)	4 (0.33)	2 (0.17)	0.34
D-/R+, n (%)	1 (0.08)	1 (0.08)	1.00
D+/R-, n (%)	2 (0.17)	4 (0.33)	0.34
D+/R+, n (%)	4 (0.33)	4 (0.33)	1.00
Delayed graft function, n (%)	4 (0.33)	1 (0.08)	0.32
Rejection therapy within previous 6 months, n (%)	3 (0.25)	5 (0.42)	0.39
Infection within previous 6 months, n (%)	6 (0.50)	5 (0.42)	0.68
Viral infection within previous 6 months, n (%)	6 (0.50)	4 (0.33)	0.41
Creatinine (µmol/L), mean ± SD	194.5 ± 70.7	185.6 ± 61.9	0.69
eGFR (mL/min/1.73m2), mean ± SD	35.8 ± 17.2	35.4 ± 22.7	0.96

*LDN: Note that the CMV serostatus was only determined for n=11 of both groups and percent values presented refer to this total number of patients.

Table 2: Immunosuppressive therapy and co-medication.

Variables	G-CSF (n=12)	No G-CSF (n=12)	p-value
Induction therapy, n (%)			
Rabbit antithymocyte globulin (rATG), n (%)	2 (0.17)	1 (0.08)	0.54
Basiliximab, n (%)	7 (0.58)	4 (0.33)	0.22
None, n (%)	3 (0.25)	7 (0.58)	0.10
Maintenance immunosuppressive therapy*			
Prednisone (mg) (n=11/12)	10.4 ± 6.1	13.4 ± 11.4	0.44
Tacrolimus, n (%)	12 (1.0)	7 (0.58)	0.12
Tacrolimus level (ng/mL) (n=7/12)	5.4 ± 2.1	6.0 ± 2.8	0.66
Ciclosporine, n (%)	0 (0.0)	2 (0.17)	0.14
Sirolimus, n (%)	0 (0.0)	2 (0.17)	0.48
Mycophenolic acid (MPA), n (%)	9 (0.75)	10 (0.83)	0.62
Mycophenolic acid (MPA) dose (mg) (n=10/9)	1,777.8 ± 441.0	1,500.0 ± 577.4	0.26
Azathioprine, n (%)	1 (0.08)	1 (0.08)	1.00
Co-medication, n (%)			
Valganciclovir, n (%)	7 (0.58)	6 (0.5)	0.68
Trimethoprime/Sulfamethoxazole, n (%)	7 (0.58)	6 (0.5)	0.68
Fluconazole, n (%)	2 (0.17)	2 (0.17)	1.00
Proton pump inhibitor, n (%)	9 (0.75)	10 (0.83)	0.62
ACE inhibitor, n (%)	1 (0.08)	4 (0.33)	0.13

*Note that the prednisone dose was determined for 11 patients of the G-CSF group. Tacrolimus level was determined for 7 patients of the G-CSF group. The MPA dose was determined for 10 patients of the G-CSF group and for 9 patients of the control group. Percent values refer to the number of patients analyzed.

a living donation with two donations from a spouse and two donations from first-degree relatives. One living donation was blood group incompatible (Table 1). The immunosuppressive therapy and co-medication were not different between groups (Table 2).

G-CSF therapy significantly shortened the mean duration of leucocytes <3,000/µL (G-CSF group: 9.5 ± 4.7 days, control group: 16.6 ± 9.3 days, p=0.02, Fig 2A). Patients with G-CSF therapy received a cumulative dose of 10.74 ± 7.84 µg/kg body weight (Table 3). The average duration of therapy was 4.3 ± 5.2 days. The leucocyte blood count was 1,247.5/µL ± 728.8/µL at the time of initiation of G-CSF therapy and 7,514.2/µL ± 7,495.1/µL, when the therapy was finished. The immunosuppressive therapy with mycophenolic acid was stopped in 8 patients of the G-CSF group and in 9 patients of the control group during the episode of leukopenia (p=0.37, Table 1). The oral immunosuppressive therapy was discontinued and switched to hydrocortisone as a continuous infusion with 200 mg/24 h in 4 patients of the G-CSF group and in 5 patients of the control group (p=0.67, Table 1).

There was a strong trend towards a higher incidence of rejections in the G-CSF group with three patients of the G-CSF group (27%) and no patient of the control group showing an acute rejection within 30 days after leukopenia (p=0.06, Table 4 and Fig 2B). Two patients developed borderline rejections and one patient showed an acute T-cell mediated and antibody-mediated rejection. All rejections were biopsy-proven. One patient also received intravenous immunoglobulin (IVIG) prior to rejection. Rejections occurred after an average of 11.00 ± 14.18 days (Table 4). All patients with rejections were treated with methylprednisolone pulse therapy and an increase of the tacrolimus trough level. The patient with antibody-mediated rejection was subjected to therapeutic apheresis. These therapies resulted in preserved graft function. One patient

Table 3: Characteristics of G-CSF therapy.

Variables	G-CSF (n=12)	No G-CSF (n=12)	p-value
Granulocyte colony-stimulating factor (G-CSF) therapy			
G-CSF cumulative dose (µg/kg body weight), mean ± SD	10.74 ± 7.84	—	—
Number of single doses, mean ± SD	2.75 ± 1.36	—	—
Duration of G-CSF therapy (days), mean ± SD	4.3 ± 5.2	—	—
Leucocytes at the beginning of G-CSF therapy (/µL), mean ± SD	1,247.5 ± 728.8	—	—
Leucocytes at the end of G-CSF therapy (/µL), mean ± SD	7,514.2 ± 7495.1	—	—
Change in immunosuppressive therapy, n (%)			
Switch to hydrocortisone therapy, n (%)	4 (0.33)	5 (0.42)	0.67
Stop of mycophenolic acid (MPA) therapy, n (%)	8 (0.67)	9 (0.75)	0.37

of each group showed biopsy-proven rejection prior and after to the episode of leukopenia and was therefore rated as a "continuous rejection" (Table 4). The cumulative dose of G-CSF had no impact on the risk of rejection (Fig 2C). No difference concerning end-stage renal disease, mortality, and graft function was observed between groups after one year. Nine patients of the G-CSF group and 8 patients of the control group showed infections in the subsequent year (p=0.65, Table 4).

DISCUSSION

Leukopenia is a common complication following kidney transplantation and is associated with increased mortality and graft loss [12]. It is mainly caused by the medication and viral infections, i.e. CMV infection. One therapeutic approach is a dose reduction and discontinuation of the most likely causative medication, such as MPA. However, this approach is associated with acute rejections [4,18,19]. The risk increases after six days of MPA discontinuation [4] and by 4% for every week of MPA dose reduction [18]. In the present study, MPA was stopped in a comparable number of patients in both groups (n=8 in the G-CSF group and n=9 in the control group, p=0.37, Table 3). An additional approach at our center is to switch the oral immunosuppression to hydrocortisone as a continuous infusion at a dose of 200mg/24hrs. This approach was performed in 4 patients of the G-CSF group and in 5 patients of the control group (p=0.67, Table 3). This indicates that patients in the G-CSF and in the control group of our study were subjected to comparable adjustments in the concomitant immunosuppressive therapy. Therefore, the differences between groups are independent of the adjustments in immunosuppressive therapy.

Stimulation with G-CSF is a therapeutic approach to shorten the total duration of leukopenia and to re-establish the standard immunosuppressive therapy more rapidly [20]. In our study, we observed a significantly reduced duration with leucocytes <3,000/µL following G-CSF therapy (Fig 2A).

Based on the adverse effects of G-CSF stimulation, which may also result in increased rejections, the safety aspect of G-CSF remains a matter of debate. Several studies show no difference in rejection rates following G-CSF [12,11,20]. However, the results are not consistent with other studies reporting acute rejections after G-CSF treatments, which typically occur during the first months. Turgeon, *et al*, describe that G-CSF therapy results in acute rejections in up to 8% of courses in kidney or liver transplant recipients within the first two months following treatment with G-CSF [10]. G-CSF also causes a significant increase in the short-term risk of rejection during the first three months after administration in heart transplant recipients [16]. In lung transplant recipients, G-CSF therapy is associated with an increased risk for chronic allograft dysfunction [17]. We observed a trend towards a higher incidence of acute rejections in kidney transplant recipients within the next 30 days following G-CSF therapy with 27% of

Table 4: Patient outcome.

Variables	G-CSF (n=12)	No G-CSF (n=12)	p-value
Acute rejection within following 30 days (n=11/11), n (%)*	3 (0.27)	0 (0.00)	0.06
Borderline rejection, n (%) (Patient #1: t2, i0; Patient #2: t1, i2)	2 (0.18)	0 (0.00)	—
T-cell mediated and antibody mediated rejection (TCMR and ABMR), n (%) (Patient #3: t2, i2, g2, ptc2, C4d**)	1 (0.09)	0 (0.00)	—
Time after G-CSF (days), mean ± SD	11.00 ± 14.18	—	—
Acute rejection within following year (n=11/11), n (%)	3 (0.27)	1 (0.09)	0.27
Continuous rejection, n (%)	1 (0.08)	1 (0.08)	1.00
Leucocytes <3,000/µL (days), mean ± SD	9.5 ± 4.7	16.6 ± 9.3	0.03*
Acute transplant failure, n (%)	7 (0.58)	6 (0.5)	0.68
Acute transplant failure and end-stage renal disease, n (%)	2 (0.17)	1 (0.08)	0.95
Creatinine after 1 year (µmol/L) (n=8/8), mean ± SD	185.6 ± 53.0	247.5 ± 123.8	0.21
eGFR after 1 year (ml/min/1.73 m2) (n=8/8), mean ± SD	37.2 ± 14.9	33.9 ± 26.3	0.77
Δ Creatinine (µmol/l), (33% data missing), mean ± SD	0.0 ± 53.6	-35.4 ± 77.8	0.32
Δ eGFR (ml/min/1.73 m2), (33% data missing), mean ± SD	37.2 ± 14.9	33.9 ± 26.3	0.96
Infection within 1 year, n (%)	9 (0.75)	8 (0.67)	0.65
Viral infection within 1 year, n (%)	2 (0.17)	5 (0.42)	0.18
Bacterial infection within 1 year, n (%)	5 (0.42)	2 (0.17)	0.18
Mortality, n (%)	1 (0.08)	3 (0.25)	0.27
Mortality due to infectious disease, n (%)	1 (0.08)	1 (0.08)	1.00

C4d: positive C4d staining; g: glomerulitis; i: interstitial inflammation; ptc: peritubular capillaritis; t: tubulitis.

*Note that acute rejections are only determined for 11 patients in both groups as one patient per group showed signs of rejection before and after the episode of leukopenia and is therefore termed "continuous rejection". Creatinine after one year was available for 8 patients per group.

C4d**: The C4d staining could not be used as a marker for the humoral rejection, as it was an ABOi living donation.

patients showing a Borderline- or combined T-cell mediated and antibody-mediated rejection (p=0.06, Fig 2B and Table 4). No patient in the control group showed signs of rejection in the same time frame. Of note, the cumulative dose of G-CSF (10.74 µg/kg ± 7.84 µg/kg) was similar compared to a previous report (11.8 ± 9.0 µg/kg), which showed no increase in rejection rate in the following month and contrasts that of our study [11].

As this is a retrospective analysis with a small number of patients we recognize the limitations of our study. In addition, limitations are based on a limited time frame and restriction to a single center. Based on the small study population, the clinical significance of this analysis should be interpreted with caution.

Together, G-CSF is a therapeutic approach to decrease the duration of leukopenia, but it may also increase the risk of an acute rejection within the first months following administration. Our data also suggest no adverse long term effects over the time frame of one year, including no difference in mortality and acute rejections. Larger prospective studies are required to assess the risk of G-CSF therapy in kidney transplant recipients.

CONFLICTS OF INTEREST: None to be declare.

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