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The impact of continuous erythropoietin receptor activators in patients after heart transplantation with multifactorial anemia with chronic kidney disease

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Abstract

Background: Multifactorial anemia with chronic kidney disease (CKD) is a common problem after heart transplantation (HTX). Erythropoiesis-stimulating agents (ESAs) are commonly used to improve hemoglobin levels in patients with anemia due to CKD. With CERA (Continuous Erythropoietin Receptor Activator) a new therapeutic agent with a longer serum half time is available. However, data in patients after HTX are extremely limited. This study retrospectively evaluated the effects of anemia treatment with CERA versus conventional ESAs (Erythropoietin beta) in patients after HTX with anemia due to CKD. Additional emphasis was put on patients' preference and adherence.

Patients and methods: A total of 20 ESA naive heart transplant recipients with anemia due to CKD were included and analyzed retrospectively. All patients had baseline hemoglobin levels below 11.0 g/dl. 10 patients (mean age 53.4 ± 10.2 years, mean time post HTX 0.7 ± 0.7 years, 9 male/1 female) were included in the CERA group and 10 patients (mean age 60.2 ± 12.9 years, mean time post HTX 5.5 ± 5.2 years, 7 male/3 female) in the conventional ESA group (Erythropoietin beta). Primary endpoint was the change in hemoglobin level from baseline to month four, eight and twelve months post initiation of either CERA or conventional ESAs. Hemoglobin target level was 12.0 g/dl. In addition, patients were asked to complete a patient self-assessment questionnaire regarding conventional ESA/CERA use.

Results: After 12 months of CERA and conventional ESA therapy, a statistically significant increase in mean hemoglobin levels was observed (CERA group: 9.0 ± 1.0 g/dl (baseline) vs. 11.8 ± 1.9 g/dl (month 12), $P=0.005$ vs. baseline, conventional ESA group 9.2 ± 1.1 g/dl (baseline) vs. 11.0 ± 2.2 g/dl (month 12), $P=0.02$ vs. baseline). In CERA patients, a continuous increase in mean hemoglobin levels was observed throughout the study period, whereas mean hemoglobin level was more fluctuant in conventional ESA patients. CERA and conventional ESA therapy were both well tolerated and no adverse events occurred during the study period. General pain level was significantly lower in the CERA group (CERA 1.9 ± 0.9 vs. conventional ESA 3.1 ± 1.0 , $P=0.03$). In the CERA group, 2 patients answered to have skipped a single CERA dose ($P=0.006$ vs. conventional ESA group), no patient had skipped multiple doses ($P=0.003$ vs. conventional ESA group). In the conventional ESA group, 9 patients had skipped a single ESA dose and 7 patients had left out multiple doses. All patients preferred a longer dosing interval ($P<0.0001$).

Conclusions: CERA therapy demonstrated a continuous increase in hemoglobin level during the study period. Longer dosing intervals were advantageous as ease of dosing was more pronounced in CERA patients and the rate of missed doses was lower in CERA patients indicating a better adherence. Our results underline the importance of optimized patient adherence by longer dosing intervals in this selected patient population with a multitude of co-medications.

Keywords: continuous erythropoietin receptor activator, anemia, heart transplantation, hemoglobin, quality of life

List of abbreviations:

CERA	Continuous Erythropoietin Receptor Activator
CKD	Chronic kidney disease
eGFR	estimated Glomerular Filtration Rate
ESA	Erythropoiesis-stimulating agent
EPO	Erythropoietin
Hb	Hemoglobin
HTX	Heart transplantation
IU	International unit
NS	Not statistically significant
P	P-value

Introduction

Anemia is a common comorbidity in patients with cardiac disease and is associated with adverse long-term outcome as multiple studies have demonstrated a correlation between reduced hemoglobin levels and impaired survival in patients with congestive heart failure [1]. But also in patients after heart transplantation (HTX) prevalence of anemia is up to 78 percent [2]. However, currently available data in patients after HTX are extremely limited, although anemia in heart failure patients is associated with an adverse outcome [3].

The World Health Organization defines anemia as hemoglobin (Hb) levels below 13.0 g/dl in men and 12.0 g/dl in women. The use of Erythropoietin (EPO) in HTX recipients with anemia due to CKD has increased over the recent years. EPO, a renal cytokine, regulates proliferation, differentiation and maturation of erythropoid blood cells. Progressive renal dysfunction leads to a decrease of EPO levels with subsequently reduced erythrocyte production in bone marrow.

In patients with anemia due to CKD, conventional ESAs are frequently used for anemia therapy [4]. In order to achieve stable levels of hemoglobin, conventional ESAs have to be applied up to three times weekly, which may negatively affect patient adherence. With CERA, a new agent is available, allowing longer dosing intervals. CERA, methoxy-polyethylene glycol-epoetin- β (Roche Pharma AG, Grenzach-Wyhlen, Germany), is a third-generation erythropoiesis stimulating agent (ESA). CERA is administered every other week to correct anemia or once monthly in the maintenance phase, i.e. hemoglobin level >11.0 g/dl. Compared to conventional ESAs, CERA has a different affinity at the receptor level and therefore has a longer serum half-life (approximately 130 hours), offering potential advantages due to less frequent administration [5-7].

In this study we retrospectively analyze effects of CERA therapy in ESA naive HTX patients with anemia due to CKD versus conventional ESA therapy. Main emphasis was put on hemoglobin levels (absolute levels and time pattern) four, eight, and twelve months after initiation of CERA treatment versus conventional ESAs. Additional emphasis was put on patient preference and adherence during EPO therapy.

Subjects and methods

Study design and patient population

This single-center study (study period 9/2010 - 1/2014) retrospectively assessed effects of anemia treatment with CERA (Mircera[®], Roche Pharma AG, Grenzach-Wyhlen, Ger-

many) versus conventional ESAs (Erythropoietin beta) in adult heart transplant recipients with anemia due to CKD (hemoglobin levels below 11.0 g/dl) during a follow-up period of 12 months.

Approval of the ethics committee of the University of Heidelberg in Germany was obtained prior to patient inclusion and written patient informed consent was obtained prior to study inclusion. Prior to study inclusion other causes of anemia than CKD were ruled out. Anemia work-up included determination of hemoglobin levels, hematocrit, serum ferritin and transferrin and three fecal occult blood detection tests.

All study patients had to be constantly followed up at the University of Heidelberg HTX center (Heidelberg, Germany) according to the center's clinical routine protocols. A complete set of demographic and clinical parameters was mandatory. In all patients, standard laboratory serology was reviewed including red and white blood cell count, thrombocytes, and renal function tests. Creatinine clearance was calculated by using the Cockcroft-Gault formula [8].

Erythropoietin treatment

10 patients were treated with CERA. Recommended starting dose was 0.6 $\mu\text{g}/\text{kg}$ body weight every second week, according to manufacturer's recommendations). 7 patients received an initial dose of 50 μg of Mircera[®] subcutaneously every other week and 3 patients were on 30 μg of Mircera[®] subcutaneously every other week as starting dose.

In the conventional ESA group, 10 patients received the recommended Erythropoietin beta starting dose of 20 IU/kg body weight three times per week. 4 patients in CERA group and 4 patients in the conventional ESA group received additional iron supplementation at baseline ($P = \text{ns}$).

Immunosuppression

As described previously, all patients received a combination of a calcineurin inhibitor and

mycophenolate mofetil as baseline immunosuppression (Cyclosporine A target trough levels post HTX: months 1–2, 175–225 $\mu\text{g}/\text{L}$; months 3–6, 125–175 $\mu\text{g}/\text{L}$; months 7–12, 110–140 $\mu\text{g}/\text{L}$, months 13–24, 90–110 $\mu\text{g}/\text{L}$, months 24 and beyond, 70–90/50–70 $\mu\text{g}/\text{L}$ [depending on rejection profile], tacrolimus target trough levels: months 1–2, 12–14 $\mu\text{g}/\text{L}$; months 3–6, 10–12 $\mu\text{g}/\text{L}$; months 7–12, 8–10 $\mu\text{g}/\text{L}$; months 13–24, 6–8 $\mu\text{g}/\text{L}$; months 24 and beyond, 4–6 $\mu\text{g}/\text{L}$ [depending on rejection profile], mycophenolate mofetil target pre-dose levels: months 1–12, 2.0–4.0 mg/L and months 12 and beyond, 1.5–2.5 mg/L) [9]. In combination with mammalian target of rapamycin inhibitors, different target levels were applied according to center standard. Steroids were routinely administered for 6 months post-HTx (complete withdrawal according to investigators' discretion whenever possible). According to center standard, induction therapy with anti-thymocyte globulin was applied in all patients. As described previously, dosage and duration of therapy were adjusted according to cluster of differentiation (CD) 4 T-cell counts monitored daily during the first week post-HTX by flow cytometry, with the aim of absolute CD4 T-cell numbers below 50/ μL [10].

Patient questionnaire

After 12 months, all patients were asked to complete a patient questionnaire regarding CERA or conventional ESA application. Patients were asked to comment on pain level associated with injection on a scale from 0 (no pain) to 10 (maximum pain), missed doses (single missed doses, multiple [i.e. more than three] missed doses), and individual preference of a longer dosing interval.

Data were collected through structured interviews. Each interview lasted approximately 10 minutes. Interviews were conducted in a private room in the outpatient department. All interviews were performed by the same investigator, while a second investigator observed and took notes.

Statistical analysis

Statistical analysis was performed with the SPSS statistical software (version 14.0, SPSS Inc., Chicago, Illinois), and a 2-sided P-value of <0.05 was considered to be statistically significant. Student t test was used for normally distributed variables and the Mann-Whitney test and Wilcoxon signed rank test for not normally distributed variables. Cate-

gorical variables were compared using the chi-square test.

Results

Study population

In the CERA group, 10 ESA naive HTX patients (mean age 53.4 ± 10.2 years, mean time post HTX 0.7 ± 0.7 years, nine

Table 1: Patient characteristics at baseline

Table 1a: Routine laboratory and clinical parameters

Parameter	Normal range	CERA (n=10)	Conventional ESA (n=10)	P-value
Hemoglobin (g/dl) (mean \pm SD)	w > 12.0, m > 13.0	9.0 (1.0)	9.2 (1.1)	P = ns
Hematocrit (l/l) (mean \pm SD)	0.38 -0.52	0.3 (0.03)	0.3 (0.03)	P = ns
Leukocytes (/nl) (mean \pm SD)	4 – 10	6.9 (3.3)	5.5 (2.2)	P = ns
Thrombocytes (/nl) (mean \pm SD)	150 - 440	247.8 (73.7)	250.9 (67.7)	P = ns
MCV (fl) (mean \pm SD)	83 - 97	84.6 (4.8)	88.3 (4.8)	P = ns
MCH (pg) (mean \pm SD)	27 - 33	27.4 (1.3)	28.9 (2.1)	P = ns
GOT (U) (mean \pm SD)	<50	19.8 (7.3)	18.8 (10.6)	P = ns
GPT (U) (mean \pm SD)	<50	22.1 (11.3)	19.3 (16.5)	P = ns
GGT (U/l) (mean \pm SD)	<60	103.8 (110.1)	50.4 (65.1)	P = ns
Heart rate (beats per minute) (mean \pm SD)	60-100	92.2 (16.8)	94.3 (15.5)	P = ns
Recipient age (years) mean (\pm SD)	na	53.4 (10.2)	60.2 (12.9)	P = ns
Male recipient gender n (% of group)	na	9.0 (90.0)	7.0 (70.0)	P = ns
Time after heart transplantation (years) (mean \pm SD)	na	0.7 (0.7)	5.5 (5.2)	P=0.01
Body weight (kg) (mean \pm SD)	na	75.3 (13.8)	60.9 (9.6)	P=0.03
BMI (kg/m ²) (mean \pm SD)	na	24.0 (4.0)	20.5 (1.7)	P=0.04

Table 1b: Donor characteristics at baseline

Parameter	CERA (n=10)	Conventional ESA (n=10)	P-value
Donor age (years) (mean \pm SD)	47.9 (13.0)	41.3 (13.0)	P=ns
Male donor gender n (% of group)	1.0 (10.0)	3.0 (30.0)	P=ns
Ischemic time (minutes) (mean \pm SD)	259.0 (78.6)	188.6 (39.9)	P=ns

Legend: BMI: body mass index, CERA: new CERA treatment, ESA: new conventional ESA treatment, GGT: Gamma-Glutamyl-Transferase, GOT: Glutamat-Oxalacetate-Transaminase, GPT: Glutamate-Pyruvate-Transaminase, MCH: mean corpuscular volume, MCV: mean corpuscular volume, n: number of patients, ns: not statistically significant, SD: standard deviation.

male/one female) with anemia due to CKD and de novo CERA therapy were analyzed. In these patients, a retrospective analysis was performed for 12 months after initiation of CERA treatment.

In the conventional ESA group, 10 ESA naive HTX patients (mean age 60.2 ± 12.9 years, mean time post HTX 5.5 ± 5.2 years, seven male/three female) were selected for "matched pairs"-analysis. These patients were treated with conventional ESA therapy. These patients were matched according to the following clinical parameters: underlying cause of anemia, renal function, hemoglobin level, indication for HTX, age (tables 1-3, all $P=ns$).

In the CERA group, indication for HTX was dilated cardiomyopathy in six patients (60.0 %), ischemic cardiomyopathy in three patients (30.0 %) and cardiac amyloidosis in one patient (10.0 %). Indication for HTX in the conventional ESA group was dilated cardiomyopathy in seven patients (70.0 %), is-

chemic cardiomyopathy in two patients (20.0 %) and amyloidosis in one patient.

Mean donor age in the CERA group was 47.9 ± 13.0 years and in the conventional ESA group 41.3 ± 13.0 years ($P=ns$). No statistically significant differences regarding donor gender were observed (female donor gender 90.0 % in the CERA group and 70.0 % in the conventional ESA group, $P=ns$). Further patient characteristics are given in tables 1-2.

Erythropoietin therapy and side effects

Mean Methoxy-Polyethylenglycol-Epoetin beta dose in CERA group after 12 months was $88.0 \pm 19.3 \mu\text{g/month}$. After 12 months, in the CERA group, seven patients (70% of total) received $50.0 \mu\text{g}$ per month and three patients (30.0% of total) $30.0 \mu\text{g}$ per month.

Mean EPO beta dose in conventional ESA group was $8500.0 \text{ IU} \pm 3374.7 \text{ IU}$ per

Table 2: Renal function at baseline and month 12

Parameter	Time-point	CERA (n=10)	Conventional ESA (n=10)	P-value
eGFR (ml/min) (mean \pm SD)	Baseline	50.9 (18.9)	39.4 (29.9)	$P=ns$
	Month 12	54.5 (12.9)	31.2 (12.1)	$P=ns$
Creatinine (mg/dl) (mean \pm SD)	Baseline	1.9 (0.6)	2.2 (0.9)	$P=ns$
	Month 12	1.8 (0.6)*	2.3 (0.6)#	$P=ns$
Urea (mg/dl) (mean \pm SD)	Baseline	52.0 (25.2)	89.7 (35.4)	$P=ns$
	Month 12	74.4 (33.5)**	87.3 (52.7)##	$P=ns$

Legend: CERA: new CERA treatment, ESA: new conventional ESA treatment, eGFR: estimated Glomerular Filtration Rate, n: number of patients, SD: standard deviation, * $P=ns$ vs. baseline, # $P=ns$ vs. baseline, ** $P=ns$ vs. baseline, ## $P=ns$ vs. baseline.

Table 3: Indications for heart transplantation

Parameter	CERA (n=10)	Conventional ESA (n=10)	P-value
CAD	3 (30.0)	2 (20.0)	$P=ns$
Dilated cardiomyopathy n (% of group)	6 (60.0)	7 (70.0)	$P=ns$
Amyloidosis n (% of group)	1 (10.0)	1 (10.0)	$P=ns$

Legend: CAD: coronary artery disease, CERA: new CERA treatment, ESA: new conventional ESA treatment, n: number of patients, ns: not statistically significant.

week. One patient (10.0% of total) received 5000.0 IU once a week, two patients (20.0 % of total) 4000.0 IU once a week, three patients (30.0 % of total) 4000.0 IU twice per week and four patients (40.0 % of total) 4000.0 IU three times per week.

Generally, CERA and conventional ESA therapy was well tolerated, as no adverse

events were observed during CERA and conventional ESA therapy during study period.

Hemoglobin levels

In the CERA group, mean hemoglobin level at baseline was 9.0 ± 1.0 g/dl (hematocrit 0.3 ± 0.03 l/l) versus 11.8 ± 1.9 g/dl after

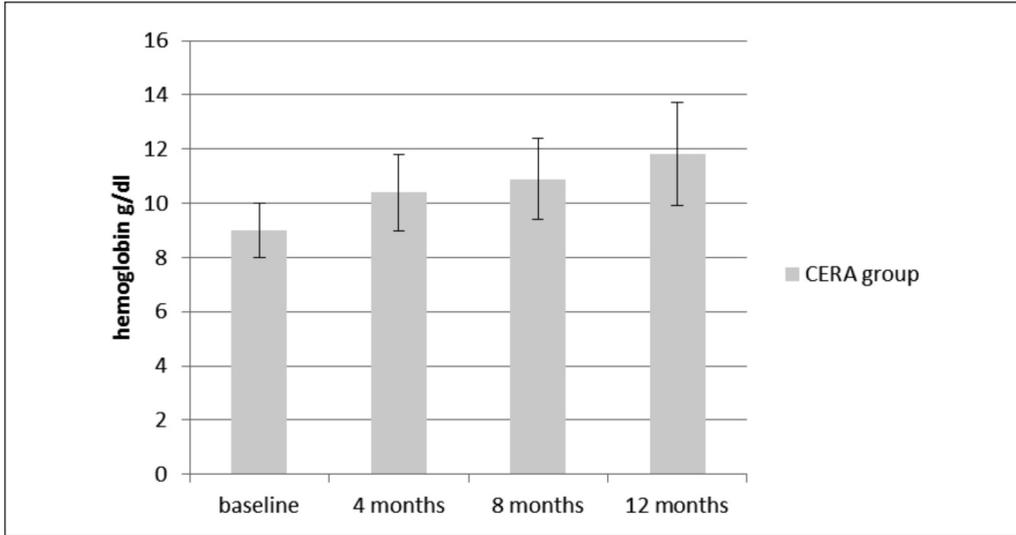


Figure 1: CERA group mean hemoglobin level at baseline and during study period (including standard deviation)

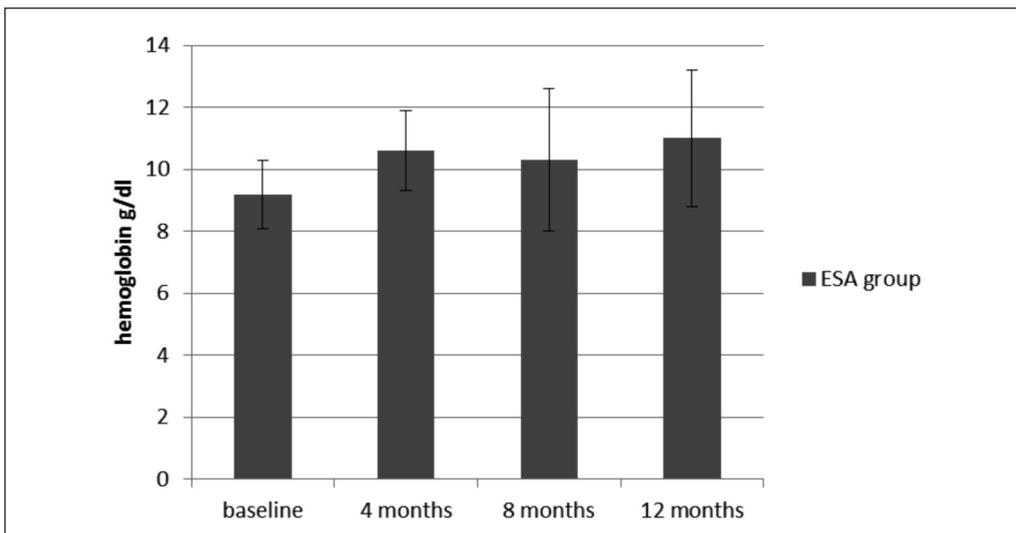


Figure 2: Conventional ESA group mean hemoglobin level at baseline and during study period (including standard deviation)

12 months (hematocrit 0.4 ± 0.1 l/l) at month 12 (hemoglobin: $P=0.005$ vs. baseline).

In the conventional ESA group, mean hemoglobin level at baseline was 9.2 ± 1.1 g/dl (hematocrit 0.3 ± 0.03 l/l) compared to 11.0 ± 2.2 g/dl (hematocrit 0.3 ± 0.1 l/l) at

month 12 (hemoglobin: $P=0.02$ vs. baseline).

In CERA patients a continuous increase in hemoglobin levels was observed during the observation period (Figures 1, 3), whereas hemoglobin levels in the conventional ESA group were more fluctuant (Figures 2, 3).

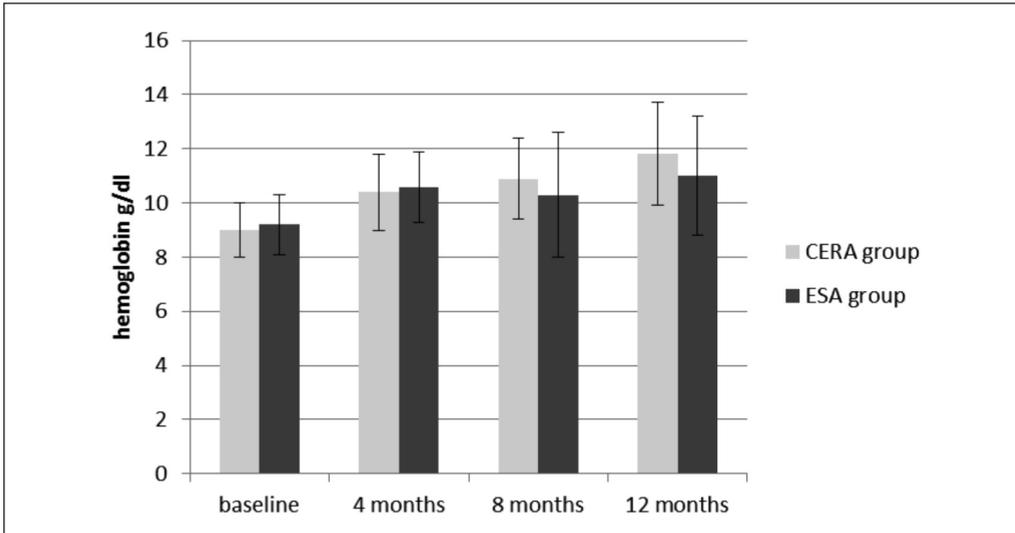


Figure 3: Mean hemoglobin level in CERA group compared to the conventional ESA group at baseline, month 4, eight, and twelve (including standard deviation)

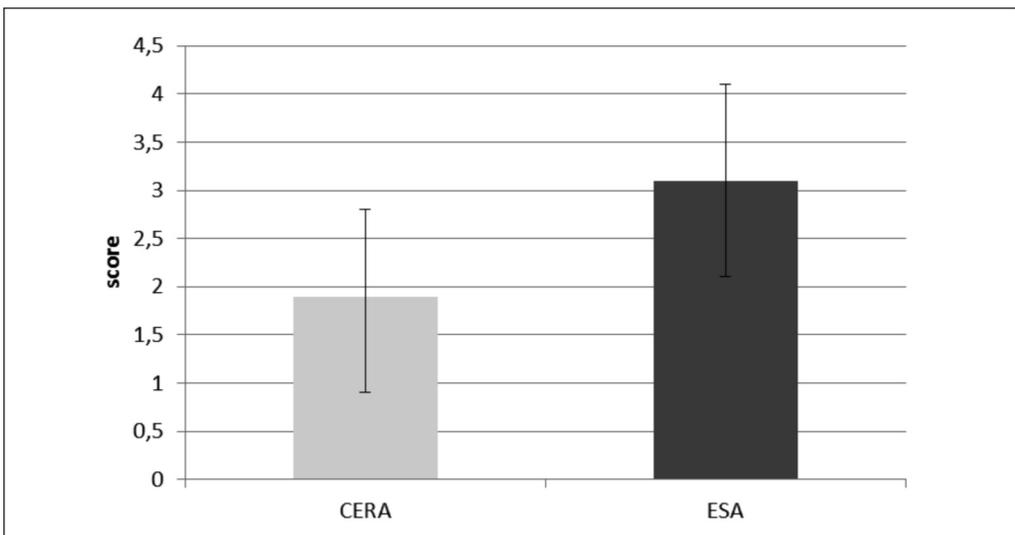


Figure 4: Mean pain level in CERA and conventional ESA group ($P=0.03$) (including standard deviation)

Routine laboratory parameters

No statistically significant differences in mean serum creatinine level and estimated Glomerular Filtration Rate (eGFR) were observed at baseline between CERA patients and patients in the conventional ESA control group (Table 2, $P=ns$). Accordingly, after 12 months of CERA or conventional ESA therapy, no statistically significant differences in mean serum creatinine level and eGFR were observed (Table 2, $P=ns$). Except from a higher urea level at baseline in CERA patients no statistically significant differences in routine laboratory parameters were observed.

Patient questionnaire

All patients were asked to complete a voluntary patient questionnaire regarding CERA or conventional ESA application (see Methods). Answers were available from all patients. Interestingly, general pain level was significantly lower in the CERA group (CERA 1.9 ± 0.9 vs. conventional ESA 3.1 ± 1.0 , $P=0.03$, Figure 4). In the CERA group 2 patients answered to have skipped a single CERA dose ($P=0.006$ vs. conventional ESA group), no patient had skipped multiple doses ($P=0.003$ vs. conventional ESA group). In the conventional ESA group 9 patients had skipped a single ESA dose and 7 patients had left out multiple doses. All patients preferred a longer dosing interval ($P<0.0001$).

Discussion

After 12 months of CERA and conventional ESA therapy a statistically significant increase in hemoglobin levels in patients after HTX with CKD was seen. No adverse events were observed during the study period. Additionally, no statistically significant differences in the remaining routine laboratory parameters were found.

It is noteworthy that a similar increase in hemoglobin level was achieved with signifi-

cantly less injections required in CERA patients. CERA and conventional ESA therapy was generally well tolerated. However, voluntary patient questionnaire clearly showed a preference towards longer dosing intervals.

Ease of dosing was more pronounced in CERA patients and the rate of missed doses was lower in CERA patients indicating a better adherence. In CERA patients, a continuous increase in mean hemoglobin level was observed throughout the study period, whereas mean hemoglobin level was more fluctuant in conventional ESA patients. This might partially be attributed to the better adherence in CERA patients.

Limitations

Our single-center pilot study is limited by the relatively small patient number of 20 participants. However, currently, there are no published data regarding CERA therapy in patients after HTX available.

However, the results of this single-center pilot study in HTX recipients are promising. Future blinded large multicenter studies are required to confirm these findings and to evaluate long-term effects regarding survival.

All interviews took place at the outpatient department. This may have affected patients' answers, as the environment might not have been convenient from the patients' perspective. However, the setting was identical for every patient.

Conclusion

In conclusion this study underlines the importance of an optimized medication schedule in patients after HTX taking a multitude of different comedication besides immunosuppression in order to warrant an optimized adherence and outcome after HTX.

Funding, conflict of interest statement

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Declaration

All human studies have been reviewed by the ethics committee of the University of Heidelberg and have therefore been performed in accordance with the ethical standards laid down in the 2008 Declaration of Helsinki.

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