Switch des anti-calcineurines au Belatacept chez les patients transplantés rénaux présentant un rejet humoral chronique-actif

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Switch from Calcineurin Inhibitors to Belatacept in Kidney Transplant patients with chronic-active Antibody Mediated Rejection results in a lower decline in Kidney Transplant function at three years.

Abbreviations

AMBR: Antibody Mediated Rejection

ca-ABMR: chronic-active Antibody Mediated Rejection

CNI: Calcineurin Inhibitors

D0: Day 0

DSA: Donor Specific Antibodies

eGFR: estimated Glomerular Filtration Rate

HR: Hazard Ratio

KT: Kidney Transplantation

MFI: Mean Fluorescence Intensity

Abstract

Introduction:

Chronic-active Antibody Mediated Rejection (ca-ABMR) in Kidney Transplant (KT) lacks effective treatment. Hence, latest guidelines recommend usual nephroprotective therapies in which limiting nephrotoxicity is paramount. Belatacept which usefulness in Extended Criteria Donors and chronic vascular changes has been shown could be an interesting alternative to Calcineurin Inhibitors (CNI). This study aims to evaluate if switch from CNI to Belatacept is beneficial on KT survival and function in ca-ABMR.

Methods:

Patients with the diagnosis of ca-ABMR and switched to Belatacept between 2012 and 2020 in four French KT centers were retrospectively included.

Results:

Nineteen patients were switched from CNI to Belatacept and compared to 58 controls with a median follow-up of 29 [4 - 125] months. Biopsy was performed 78 [4 - 140] months after KT, with a mean estimated Glomerular Filtration Rate (eGFR) of 36.2 ± 15.6 mL/min/1.73m^2.

There was no difference of eGFR at baseline, one, two and three years: 31.2 ± 14.5, 26.0 ± 19.7, 22.4 ± 19.5 and 22.1 ± 24.9 mL/min/1.73m^2, respectively, in the Belatacept-treated group, versus 36.1 ± 15.7, 29.1 ± 18.6, 23.4 ± 18.0 and 17.5 ± 18.0 mL/min/1.73m^2 in the CNI-treated group. The delta of eGFR between 3 years and Day 0 was -9.1 ± 14.3 mL/min/1.73m^2 in the Belatacept-treated group versus -18.6 ± 15.1 mL/min/1.73m^2, p = 0.05. This difference was increased when focusing on the subgroup with a baseline eGFR ≥ 35 mL/min/1.73m^2: 3.3 ± 19.2 versus -25.3 ± 17.1 mL/min/1.73m^2, p = 0.005. However, death-censored survival was similar in the two groups at one, two and three years: 81.3%, 71.4% and 41.6%, respectively, in the Belatacept-treated group, versus 84.4%, 66.0% and 47.1%, p = 0.6.

Conclusion:

Switch from CNI to Belatacept may lower decline of eGFR at three years, especially when it is started at an early stage. However, it does not appear to have an effect on death-censored KT survival.

Introduction

Despite advances in management of Antibody Mediated Rejection (ABMR) in Kidney Transplant (KT) patients, it still remains a major cause of estimated Glomerular Filtration Rate (eGFR) alteration and graft loss (1). Human Leukocyte Antigen (HLA) and non-HLA mismatch between the donor and the recipient ultimately leads to the genesis of specific B cells through the B cell – T follicular helper crosstalk. Alloreactive B cells then differentiate into a diverse panel of alloreactive B cells according to their affinity for the donor molecules and to their lifespan. Once activated, these alloreactive B cells are responsible for the production of Donor Specific Antibodies (DSA) which bind the donor endothelial cells. This leads both to the activation of the complement classical pathway, and to the recruitment of innate immune cells. These two pathways are responsible for the aggression of endothelial cells, including mononuclear cell infiltration, smooth muscle cell proliferation and duplication of glomerular basement membrane, thus ultimately resulting into an allograft vasculopathy (2), the canonical lesion of chronic-active ABMR (ca-ABMR).

Another source of chronic endothelial damages in the scope of KT is the use of Calcineurin Inhibitors (CNI). Although CNIs use was a major breakthrough for KT survival and function, the acute and chronic nephrotoxicity of these drugs is now a hindrance at a time of grafts shortage and increasing number of expanded criteria donors.

Therefore, Belatacept, a co-stimulation blockade molecule, has emerged as an interesting alternative which has demonstrated its interest in situations where graft endothelium is impaired in order to improve long term eGFR, such as Extended – Criteria Donors and chronic vascular changes (3,4). Moreover, recent studies allow to broaden the indication of Belatacept to patients with a high immunological risk (5) with benefits in reducing DSA titer (6,7).

Considering these endothelial and immunological effects, this retrospective multicentric study was conducted in order to assess the beneficial effect on KT function and survival of a switch

from CNI to Belatacept in case of ca-ABMR, in which chronic production of DSA leads to chronic endothelial lesions.

Material and methods

Study population

Based on pathology databases from four different French Kidney Transplant centers (Angers, Grenoble, Paris-Creteil, Rouen), all biopsies, protocol and for cause, performed between January 2007 and January 2020 were screened and selected when they met all ca-ABMR diagnosis criteria according to Banff 2019 classification (8): (1) transplant glomerulopathy (cg>0) with no evidence of chronic thrombotic microangiopathy of glomerulonephritis or arterial intimal fibrosis of new onset, (2) linear C4d staining > 1 by immunofluorescence or > 0 by immunohistochemistry, or microvascular inflammation defined by g + ptc ≥ 2 and (3) serologic evidence of DSA or C4d staining. All patients from with the diagnosis of ca-ABMR and switched to Belatacept were included. Control group consisted in all patients from Rouen's pathological database with histological diagnosis of ca-ABMR who remained on CNI. When several biopsies were available for one patient, only the first biopsy with the diagnosis of ca-ABMR was included. Patients whose follow-up was less than three months were excluded. Informed consent was obtained for all patients included in the study.

Belatacept administration

Before the switch to Belatacept, patients had to be seropositive for Epstein-Barr Virus. Belatacept was administered intravenously according to previously published protocol: 5 mg/kg every two weeks for five injections, then 5mg/kg every month (9). CNI were gradually reduced until discontinuation at the end of the first month.

Data collection

KT function was evaluated by eGFR according to MDRD formula (10). In the Belatacept-treated group, Day 0 (D0) was the day of first administration of Belatacept. In the control group, D0 was the day of the biopsy. Data were collected from 3 months before D0, then every 3 months for one year, then once a year until KT failure: return to dialysis, retransplantation or death. In three centers, DSA were monitored once a year with Luminex as a screening test and a single antigen beads solid phase assay (Labscreen; One Lambda) in case of positivity. The threshold for positivity was a Mean Fluorescence Intensity (MFI) above 500. In the last center, the Immucor Lifecodes test was used with a positivity threshold of Background Corrected MFI of 2000.

Statistical analysis

Quantitative data are presented with mean ± standard deviation (SD) or median with [min - max] according to their distribution. Qualitative data are presented with number of patients and percentages. The chi-squared test was used for categorical variables, the Student's test and the Mann-Whitney U test were used for continuous variables. KT survival was assessed using Kaplan-Meier curves and log rank test. Cox proportional hazards regression was used to assess the association between KT survival and clinical, biological or pathological characteristics. A two-sided p-value < 0.05 was considered statistically significant. Due to the low number of patients monitored with Immucor (N=2), they were excluded from statistical analysis concerning DSA. Statistical analyses were conducted using GraphPad Prism version 6.04, GraphPad Software, La Jolla California USA.

Results

Patients characteristics.

Nineteen patients were switched from CNI to Belatacept post ca-ABMR and compared to 58 controls patients, with a median follow-up of 29 [4 - 125] months post conversion (figure 1).

Median age at the time of the biopsy was 49 [19 - 76] years old. Biopsy was performed 78 [4 - 140] months after KT, with mean eGFR 36.2 ± 15.6 mL/min/1.73m^2 and proteinuria/creatininuria ratio 1.3 ± 1.3 g/g. In the entire cohort, pathology score was cg = 1.8 ± 0.8, g + ptc = 3.0 ± 1.1, ci + ct = 2.6 ± 1.5 and cv + ah = 2.8 ± 1.3. Characteristics of patients between the Belatacept-treated group and CNI-treated group are detailed in table 1. Banff score was comparable between the two groups except for tubulitis: 0.4 ± 0.8 in the Belatacept-treated group versus 0.1 ± 0.2 in the control group (p = 0.02), and [g + ptc] score: 2.6 ± 0.8 in the Belatacept-treated group versus 3.4 ± 1.1 (p = 0.007). In the Belatacept-treated group, 43.1% of patients had a previous biopsy with the diagnosis of active ABMR treated by plasmapheresis, rituximab and intravenous immunoglobulins versus 25.9% in the CNI-treated group (p = 0.2). Despite those differences, the two groups were similar in age, eGFR and proteinuria/creatininuria ratio at baseline. In the Belatacept-treated group, there was a statistically significant decline in the MFI of immunodominant DSA from 4298 ± 3912 to 2046 ± 2701 at one year (p = 0.03), versus a relative stability in the CNI-treated group: 4929 ± 5265 to 4160 ± 4586, p = 0.2.

Graft survival in all the cohort and risk factor for graft loss.

There was only one death in the control-group, with functioning KT. There was no acute rejection in any group. At one, two and three years, death-censored KT survival in the Belatacept-treated group was 81.3%, 71.4% and 41.6% versus 84.4%, 66.0% and 47.1% in the CNI-treated group, p = 0.6.

Using Cox regression, univariate analysis showed that the switch from CNI to Belatacept was not protective from graft loss, p = 0.6. In univariate analysis, characteristics associated with a worst KT survival were cg, [ci + ct] and cv scores with a p-value of 0.003, 0.003 and 0.0006, respectively (table 2). The eGFR at the time of the biopsy was also significantly associated with

KT survival, p = 0.002. The proteinuria/creatininuria ratio was almost statistically significant (p = 0.06). In multivariate analysis, cg and cv scores were statistically associated with graft loss Hazard Ratio (HR) = 2.21 [1.37 – 3.55], p = 0.01 and 1.92 [1.24 – 2.96], p = 0.003, respectively, while high eGFR at the time of the biopsy was protective: HR = 0.96 [0.94 – 0.99], p = 0.004.

Graft function at one and two years.

Eighteen patients in the Belatacept-treated group and 58 patients in the CNI-treated group were evaluated at the 12-month endpoint. Clinical and biological characteristics between groups were similar at baseline, with an eGFR = 34.1 ± 14.5 mL/min/1.73m^2 versus 35.7 ± 14.9 mL/min/1.73m^2, p = 0.7. There were statistically significant differences concerning Banff score: ah score = 1.7 ± 1.3 in the Belatacept-treated group versus 1.1 ± 0.9 in the CNI-treated group (p = 0.03), and [i + t] score = 0.7 ± 1.2 versus 1.2 ± 0.9 (p= 0.05). At 3 and 6 months, eGFR value in the two groups was similar: 35.9 ± 20.0 mL/min/1.73m^2 then 33.3 ± 19.0 mL/min/1.73m^2 in the Belatacept-treated group and 35.3 ± 13.0 then 33.6 ± 15.3 in the CNI-treated group. At 1 year, eGFR in the Belatacept-treated group was 30.1 ± 17.8 mL/min/1.73m^2 versus 29.1 ± 17.4 mL/min/1.73m^2, p = 0.6. Decline in eGFR between 1 year and Day 0 was statistically significant in the CNI-treated group (p = 0.03) but not in the Belatacept-treated group (p = 0.5), figure 2.

At two years, data were available for 15 patients in the Belatacept-treated group and 53 patients in the CNI-treated group. At baseline, ah score was statistically different:1.8 ± 1.3 and 1.1 ± 1.1, respectively (p = 0.03). The [g + ptc] score was also statistically different: 2.6 ± 0.8 in the Belatacept-treated group versus 3.2 ± 1.0 in the CNI-treated group, p = 0.03. In the Belatacept-treated group, baseline eGFR was 34.7 ± 15.7 versus 36.0 ± 15.3 in the CNI-treated group, p = 0.8. In the Belatacept-treated group, eGFR at 12 and 24 months were 29.5 ± 19.3 and 27.1 ± 19.8, respectively, compared to 28.8 ± 18.1 and 23.4 ± 17.5 in the CNI-group at the same

endpoints. These differences did not reach statistically significance. However, decline in eGFR at 1 and 2 years in the CNI-treated group was significant: p = 0.03 and p = 0.0001, respectively. Decline in eGFR in the Belatacept-treated group was not statistically significant.

Graft function in patients with a 36-month follow-up.

The 36-month data were available for 12 Belatacept-treated patients and 50 CNI-treated patients. Following switch to Belatacept, eGFR declined from 31.2 ± 14.5 mL/min/1.73m^2 to 26.0 ± 19.7 mL/min/1.73m^2 at one year, 22.4 ± 19.5 mL/min/1.73m^2 at two years and 22.1 ± 24.9 mL/min/1.73m^2 at three years. Comparatively, eGFR in the control group declined from 36.1 ± 15.7 mL/min/1.73m^2 at biopsy to 29.1 ± 18.6 mL/min/1.73m^2 at one year, 23.4 ± 18.0 mL/min/1.73m^2 at two years and 17.5 ± 18.0 mL/min/1.73m^2 at three years. There was no difference when comparing the two groups at one year (p = 0.7), two years (p = 0.8) and three years (p = 0.9). The delta of eGFR between 1 year and D0 was -5.1 ± 8.6 mL/min/1.73m^2 in the Belatacept-treated group versus -7.1 ± 13.3 mL/min/1.73m^2 in the CNI-treated group, p = 0.6. The delta of eGFR between 2 years and D0 was -8.8 ± 9.3 mL/min/1.73m^2 versus -12.8 ± 13.9 mL/min/1.73m^2, p = 0.3. The delta of eGFR between 3 years and D0 were -9.1 ± 14.3 mL/min/1.73m^2 versus -18.6 ± 15.1 mL/min/1.73m^2, p = 0.05 (figure 3).

Graft survival and function according to transplant glomerulopathy (cg).

In order to assess the impact of Belatacept in several conditions, subgroups were defined according to results from the Cox analysis. In the Belatacept-treated group, there were 5 (41.7%) patients with a transplant glomerulopathy score cg < 2 versus 17 (34.0%) patients in the control group. Baseline eGFR in the Belatacept-treated group and control group were 36.6 ± 15.8 mL/min/1.73m^2 versus 39.7 ± 18.4 mL/min/1.73m^2 (p = 0.7). Banff scores were not statistically different except for g score = 0.8 ± 0.4 in the Belatacept-treated group versus 1.6 ±

0.7 in the CNI-treated group, p = 0.03. In patients with cg< 2, there was no difference regarding death-censored KT survival at 1, 2 and 3 years: 85.7%, 83.3% and 60.0% in the Belatacept-treated group, respectively, versus 100.0%, 76.5% and 70.6% in the CNI-treated group, p = 0.9. In the Belatacept-treated group, eGFR was 30.5 ± 21.8 mL/min/1.73m^2 at 1 year, 27.0 ± 22.2 mL/min/1.73m^2 at 2 years and 28.8 ± 30.6 mL/min/1.73m^2 at 3 years versus 38.3 ± 21.1 mL/min/1.73m^2, 33.3 ± 22.5 mL/min/1.73m^2 and 29.9 ± 23.7 mL/min/1.73m^2 in the control group. These differences were not different at these three endpoints, p = 0.5, p = 0.6, p = 0.8, respectively.

In the subgroup with cg ≥ 2, there was no difference at baseline with an eGFR = 28.7 ± 14.9 mL/min/1.73m^2 in the Belatacept-treated group versus 34.3 ± 14.1 in the CNI-treated group, p = 0.4. There was no statistical difference in terms of KT survival: 77.8%, 62.5% and 28.6% versus 76.3%, 61.1% and 35.3%, p = 0.7. eGFR at 1, 2 and 3 years within two groups were not statistically different: 22.7 ± 19.0 mL/min/1.73m^2, 19.2 ± 18.3 mL/min/1.73m^2 and 17.3 ± 21.4 mL/min/1.73m^2 versus 24.3 ± 15.4 mL/min/1.73m^2, 18.2 ± 12.7 mL/min/1.73m^2 and 11.2 ± 9.5 mL/min/1.73m^2, with p = 0.8, p = 0.9, p = 0.9, respectively. In the Belatacept-treated group, the delta of eGFR between year 3 and D0 was -11.6 ± 10.4 mL/min/1.73m^2 versus -23.1 ± 15.0 mL/min/1.73m^2, p=0.06. The other values for delta of eGFR at one, two and three years are summarized in table 3.

Graft survival and function in case of CNI toxicity.

To assess the potential benefit of Belatacept in case of CNI toxicity, analyses were performed after focusing on patients with a [ci + ct] score ≥ 4 OR a [cv + ah] score ≥ 4 with 8 (66.7%) patients in the Belatacept-treated group and 24 (48.0%) patients in the control group. There was no difference at baseline, with an eGFR at 27.9 ± 13.5 mL/min/1.73m^2 in the Belatacept-treated group versus 29.3 ± 12.3 mL/min/1.73m^2 in the CNI-treated group (p = 0.7). Death-censored

KT survival in the Belatacept-treated group at 1, 2 and 3 years was 70.0%, 62.5% and 25% versus 70.4%, 52.0% and 37.5% in the control group, without statistically significant difference, p = 0.8.

In the Belatacept-treated group, eGFR at 1, 2 and 3 years was 21.9 ± 19.2 mL/min/1.73m^2, 21.2 ± 21.7 mL/min/1.73m^2, and 20.4 ± 29.1 mL/min/1.73m^2, respectively, versus 21.4 ± 14.0 mL/min/1.73m^2, 17.2 ± 13.5 mL/min/1.73m^2 and 13.4 ± 12.8 mL/min/1.73m^2 in the control group. Differences between groups were not statistically significant: p = 0.8, p = 0.8 and p = 0.8, respectively (figure 4). Although not statistically significant, in the Belatacept-treated group, eGFR delta between 3 years and Day 0 was -7.6 ± 17.7 mL/min/1.73m^2 versus -15.9 ± 10.8 mL/min/1.73m^2 in the CNI-treated group, p = 0.1.

Graft survival and function according to transplant arteriopathy (cv).

In the Belatacept-treated group, 8 (66.7%) patients had a cv score of 0 or 1 versus 28 (56.0%) patients in the CNI-treated group. Baseline eGFR was not different: 37.6 ± 13.2 mL/min/1.73m^2 versus 40.2 ± 16.3 mL/min/1.73m^2, p = 0.8. However, mean [ci + ct] score was 3.0 ± 1.7 in the Belatacept-treated group versus 1.8 ± 1.2 in the other group, p = 0.02. There was no difference of death-censored KT survival in the two groups. Mean eGFR at one year in the Belatacept-treated group was 33.2 ± 20.0 mL/min/1.73m^2 versus 37.1 ± 18.2 mL/min/1.73m^2, p = 0.8. At two years, eGFR = 28.7 ± 21.1 mL/min/1.73m^2 versus 30.1 ± 18.7 mL/min/1.73m^2, p = 0.9, and at three years: 30.6 ± 27.0 mL/min/1.73m^2 versus 22.5 ± 20.4 mL/min/1.73m^2, p = 0.6. The eGFR delta between 3 years and Day 0 was -7.3 ± 17.5 mL/min/1.73m^2 in the Belatacept-treated group versus -17.8 ± 17.5 mL/min/1.73m^2 in the CNI-treated group, p = 0.1.

In groups defined by cv score at 2 or 3, eGFR at baseline was different: 20.2 ± 1.7 mL/min/1.73m^2 in the Belatacept-treated group versus 30.9 ± 13.5 mL/min/1.73m^2 in the CNI-treated group, p = 0.03. This difference decreased over time: 11.5 ± 7.7 mL/min/1.73m^2 in the

Belatacept-treated group versus 18.9 ± 13.6 mL/min/1.73m^2 at one year, p = 0.3 and 10.0 ± 6.1 mL/min/1.73m^2 versus 14.8 ± 13.0 mL/min/1.73m^2 at two years, p = 0.8. At three years, all the 4 patients in the Belatacept-treated group encompassed KT loss at three years versus 72.7% in the CNI-group.

Graft survival and function according to baseline eGFR.

Median eGFR at D0 was 34.4 [12.5 – 79.7]. To determine whether the switch to Belatacept could be beneficial in early-stage of ca-ABMR, analyses were performed according to the eGFR with a cut-off of 35.0 mL/min/1.73m^2.

When focusing on the 4 (33.3%) patients and 24 (48.0%) controls with baseline eGFR ≥ 35.0 mL/min.1.73m^2, there was no difference at baseline between groups except in the cg score: 1.3 ± 1.0 in the Belatacept-treated group versus 2.3 ± 0.8 in the CNI-treated group, p = 0.03. Baseline eGFR were 49.3 ± 3.0 mL/min/1.73m^2 versus 49.4 ± 11.5 mL/min/1.73m^2, p = 0.8.

In the Belatacept-treated group, eGFR at one, two and three years was 50.6 ± 5.5 mL/min/1.73m^2, 47.0 ± 10.2 mL/min/1.73m^2, and 52.9 ± 18.4 mL/min/1.73m^2, respectively. In the CNI-treated group eGFR at the same endpoints was 39.5 ± 19.1 mL/min/1.73m^2, 33.1 ± 18.6 mL/min/1.73m^2 and 24.2 ± 22.0 mL/min/1.73m^2. These differences failed to reach statistically significance at one year (p=0.08) and two years (p = 0.07). However, at three years, p value was 0.03. More, between 1 year and Day 0, the eGFR delta was 1.3 ± 7.9 mL/min/1.73m^2 in the Belatacept-treated group versus -10.0 ± 16.4 mL/min/1.73m^2 in the other group, p = 0.2, Between 2 years and Day 0: -2.5 ± 12.2 mL/min/1.73m^2 versus -16.4 ± 16.5 mL/min/1.73m^2, p = 0.1. This difference reached statistically significance between 3 years and Day 0: 3.3 ± 19.2 mL/min/1.73m^2 versus -25.3 ± 17.1 mL/min/1.73m^2, p = 0.005. Death-censored KT survival was not different between groups, p = 0.2 (figure 5).

When considering patients with an eGFR < 35 mL/min/1.73m^2, there was no difference in baseline characteristics between groups. In the Belatacept-treated group, eGFR was 23.6 ± 7.6 mL/min/1.73m^2 at baseline, 13.7 ± 8.5 mL/min/1.73m^2 at one year, 10.2 ± 5.8 mL/min/1.73m^2 at two years and 6.7 ± 4.7 mL/min/1.73m^2 at three years. In the CNI-treated group, eGFR at the same time was 23.8 ± 6.0 mL/min/1.73m^2, 19.5 ± 12.0 mL/min/1.73m^2, 14.4 ± 11.9 mL/min/1.73m^2 and 11.4 ± 10.3 mL/min/1.73m^2, respectively. There was no statistically significant difference: p = 0.5, p = 0.2, p = 0.5, p = 0.2, respectively. Death-censored KT survival was also not different between the two groups, p = 0.6.

Discussion

This study aim was to assess the use of Belatacept in the setting of ca-ABMR post KT. Although mean eGFR was not statistically different between groups at 1, 2 and 3 years, switch to Belatacept resulted in a lower decline in eGFR than CNI. However, no evidence of a beneficial effect on death-censored KT survival was shown. Interestingly, DSA MFI in Belatacept-treated group decreased, versus stability in CNI-treated group. Secondary analyses were performed according to subgroups defined by identified risk factors for graft loss: cg and cv scores, baseline eGFR. Those analyses highlighted that the switch to Belatacept is of major interest when it is performed at an early stage with an eGFR ≥ 35 mL/min/1.73m^2, while this effect was not found on patients with transplant vasculopathy or transplant glomerulopathy.

Finally, switch to Belatacept-based regimen in case of CNI-toxicity added to ca-ABMR lesions may slow down the eGFR degradation, but to a lesser extent than in case of CNI-toxicity alone known from other studies.

To date, rejection remains the first cause of graft dysfunction, responsible for almost 50% of KT losses (1). Among types of rejection, ABMR is the major subtype leading to KT loss. The common feature of ca-ABMR is chronic vascular lesions resulting from endothelial aggression. Indeed, recognition of donor's HLA or minor histocompatibility antigens molecules expressed

on graft endothelium by the recipient's immune system induces vascular recruitment of immune effectors and complement activation (11,12). As a result endothelial cell damage occurs, with manifestations on both the micro and the macrocirculation: multilamination of the peritubular capillary, reduplication of glomerular basement membrane and fibrointimal thickening of renal arteries (13,14). Those lesions occur after a prior active ABMR (15–17), leading to irreversible transplant glomerulopathy which is associated with dismal KT prognosis (18–20). Indeed, despite reduction in DSA titer which can be reached through therapies including plasma exchange (21), Rituximab (22), or proteasome inhibitors such as Bortezomib (23), these combinations failed to demonstrate efficacy in preventing KT loss of function in the scope of ca-ABMR. Therefore, and according to latest guidelines, the aim when managing ca-ABMR is rather to stabilize KT function and limiting its degradation through usual nephroprotective therapies than to increase risks of an over-immunosuppression with therapies of unproven efficacity (24).

Belatacept is now widely used in KT, since its benefit on KT function and KT and patient survival has been proven in the BENEFIT study (25). This co-stimulation blockade molecule is known for its inhibitory activity on humoral response through the inhibition of B cell – TFh cell crosstalk (26), leading to a decreased number of activated B cell and therefore, less DSA-secreting plasma cells (27). This has been confirmed in human KT studies, and Belatacept indications have been successfully extended to immunized KT recipients (5,28), CNI-intolerant recipients from extended-criteria donors (3), and as a rescue therapy in recipients with severe vascular lesions, i.e late switch (4). Finally, it also has been shown that Belatacept-treated patients with stable function have less inflammatory and fibrogenic cells with less tubular atrophy and interstitial fibrosis as compared to CNI-treated patients (29).

Based on those studies, the hypothesis of the benefit of Belatacept on vascular and fibrotic KT secondarily to ca-ABMR was made. Although this is a retrospective study, this multicentric cohort has characteristics comparable to several studies with larger population, both in their baseline characteristics and the control group outcome (22,30,31), with a mean cg score at 1.8 ± 0.8, [ci + ct] = 2.6 ± 1.5 and cv + ah = 2.8 ± 1.4, reflecting usual practices.

Recently, Kumar et al. reported their experience of Belatacept in ca-ABMR, diagnosed by standard histologic and molecular assessment (32). In this work, the switch to Belatacept improved the eGFR at 1 year compared to a propensity matched control cohort treated by CNI in which slope of decline in eGFR remained stable. Here, a such clear improvement has not been observed. This could be partially explained by a higher [ci + ct] score in their control group (4.63 ± 1.99 versus 3.16 ± 0.89, $p < 0.01$) which could worsen the eGFR evolution in this group and emphasized differences between groups. More, their much higher death-censored graft survival at 89% at 29 months versus 65% in the current study may reflect, in addition to a better evolution with Belatacept than CNI, differences in baseline characteristics of these two populations. Finally, the use of molecular assessment in the study of Kumar et al. may provide earlier diagnosis before the occurrence of irreversible histological lesions and therefore gives the opportunity of an early treatment, which is in line with the better outcomes reported when Belatacept is started when eGFR $\geq$ 35 mL/min/1.73m^2.

Despite immunological effects of Belatacept leading to a reduced DSA titer (6,7,33), which was also found in this study, there was no group of patient defined by cg score in which Belatacept could be a viable alternative to slow down KT function degradation. Indeed, and as mentioned above, this pathological pattern is irreversible and lowering DSA level does not seem to limit it aggravation, highlighting again the major interest of an early diagnosis and treatment of active ABMR, before the occurrence of transplant glomerulopathy.

The more surprising fact is the limited benefit of the switch in patients with vasculopathy or CNI toxicity associated with ca-ABMR. Indeed, in previous study (4), withdrawal of CNI in case of CNI toxicity and/or chronic vasculopathy without active or ca-ABMR was associated with an increasing eGFR around 7 mL/min/1.73m^2 at one year versus a loss of 3 mL/min/1.73m^3 in patients who remained on CNI. More, this effect might be more significant in patients with cv score $\geq$ 2 as compared to patients with cv < 2 (34). Finally, there are arguments for an improvement in arterial stiffness and global cardiovascular risk factor with Belatacept as compared to other immunosuppressives regiments (35).

Here, the adjunction of an immunological factor on chronic vasculopathy erases the benefit of the nephrotoxicity relief occurring after CNI discontinuation. This highlights the two physiological processes in KT vasculopathy. On the one side, CNI-treated patients who undergo endothelial damage and vasoconstriction through endothelin production, reactive oxygen species and renin-angiotensin system activation system (36,37) may benefit from CNI discontinuation, both through the cessation of vasoconstriction of the afferent arterioles and reversal of molecular pathways alterations due to CNI. On the other side, fibroproliferative vasculopathy associated to rejection is characterized by mononuclear cell infiltrate and smooth muscle cell proliferation secondary to HLA molecule binding on endothelial cell surface (38,39) which evolves on its own, independently from CNI-associated vasculopathy. Consequently, the occurrence of chronic vascular changes secondary to ca-ABMR on previously healthy arteries free of CNI lesions may not be modified by CNI withdrawal. Beside this, in cases where ca-ABMR occurs on previously CNI-damaged vessels, the rapidity of fibroproliferative process induced by ca-ABMR associated with the dismal KT may exceed both in severity and speed the evolution of CNI-toxicity, thereby masking the known benefits

of Belatacept. In other words, the hypothesis in which the endothelium already aggressed by ca-ABMR may benefit from the switch to Belatacept in order to prevent another aggression by CNI toxicity remains to be established. Finally, the different outcomes in this cohort compared to previously published data on vascular and fibrotic KT (4,5), although immunological context differs, raises the question of the apprehension of KT vasculopathy. Considering that Banff criteria remain non-specific, it may be possible that some KT with vasculopathy do not meet ca-ABMR criteria although an immunological process is ongoing, and therefore could be put forward as candidates for a switch to Belatacept, which would not be beneficial according to this study. In the era of precision medicine, these considerations may be another argument for the need to develop everyday diagnostic and classification tools, for example molecular biology, in order to better select patients who may benefit from a switch to Belatacept (40).

This study encompasses several limitations due to its retrospective design and the number of patients included in the Belatacept-treated group. This is in line with the size of other clinical studies on Belatacept, and symptomatic of a still limited access to co-stimulation blockade agents in all KT centers, as evidenced by the multicentric inclusion performed. However, the main characteristics of the patients, both clinical and pathological, reflect usual practices faced by the clinician. Another strength of the study is the three years follow-up making possible to get closer to usual practices and therapeutic challenges of ca-ABMR: delaying KT function decline as long as possible. At last, this study points the lack of benefit when eGFR is already severely impaired, which deserves a particular attention, and may help to avoid switches to Belatacept that will not improve KT function but will expose the patient to complications, as opportunistic infections (41).

Conclusion

In the scope of ca-ABMR in KT, switch from CNI to Belatacept may be beneficial on KT function at three years by lowering its decline at 1, 2 and 3 years, especially when it is started at an early stage with an eGFR ≥ 35 mL/min/1.73m^2. However, it does not appear to have an effect on death-censored KT survival.

Figure legends

Figure 1: flowchart. ca-ABMR: chronic-active Antibody Mediated Rejection. CNI: Calcineurin Inhibitors.

Figure 2: Kidney Transplant (KT) function after switch from Calcineurin Inhibitors (CNI) to Belatacept. In the Belatacept-treated group, Day 0 (D0) is the day of the switch. In the CNI-treated group, D0 is the day of the biopsy. Up: KT function at one year. In the Belatacept-treated group, there was no statistically significant difference between D0 and 1 year while this difference was significant in the CNI-treated group: alteration of eGFR from 35.7 ± 14.9 mL/min/1.73m^2 to 29.1 ± 17.4 mL/min/1.73m^2, p = 0.03. ca-ABMR: chronic-active Antibody Mediated Rejection, eGFR: estimated Glomerular Filtration Rate, CNI: Calcineurin Inhibitors.

Figure 3: Death-censored Kidney Transplant (KT) survival and evolution of eGFR at 3 years after switch from Calcineurin Inhibitors (CNI) to Belatacept. KT survival was not statistically different between groups. eGFR between groups were not statistically different at these endpoints. Decline in KT function, represented by the delta of eGFR between 3 years and Day 0, was higher in the CNI-treated group: -18.6 ± 15.1 mL/min/1.73m^2 versus - 9.1 ± 14.3 mL/min/1.73m^2, p = 0.05. ca-ABMR: chronic-active Antibody Mediated Rejection, eGFR: estimated Glomerular Filtration Rate, CNI: Calcineurin Inhibitors.

Figure 4: Death-censored Kidney Transplant (KT) survival and evolution of eGFR at 3 years after switch from Calcineurin Inhibitors (CNI) to Belatacept in patients with pathological signs of CNI-toxicity, defined by a [ci + ct] score ≥ 4 OR [cv + ah] score ≥ 4. Death-censored KT survival was not different between groups (p = 0.08). Although not statistically significant, decline in eGFR in the CNI-treated group was higher than decline in the Belatacept-treated

group. ca-ABMR: chronic-active Antibody Mediated Rejection, eGFR: estimated Glomerular Filtration Rate, CNI: Calcineurin Inhibitors.

Figure 5: Death-censored Kidney Transplant (KT) survival and evolution of eGFR at 3 years after switch from Calcineurin Inhibitors (CNI) to Belatacept according to baseline.

In the analyses with a baseline eGFR < 35 mL/min/1.73m^2, Death-censored KT survival was not different between groups. The two groups encompassed severe decline in eGFR across years.

In the analyses with a baseline eGFR ≥ 35 mL/min/1.73m^2, Death-censored KT survival was not statistically different between groups (p = 0.2). In the Belatacept-treated group, eGFR was stable during the follow-up: Delta 3 years – Day 0 = 3.3 ± 19.2 mL/min/1.73m^2, while patients in the CNI-treated group encompassed severe decline in eGFR: delta 3 years – Day 0 = -25.3 ± 17.1 mL/min/1.73m^2, p = 0.005. ca-ABMR: chronic-active Antibody Mediated Rejection, eGFR: estimated Glomerular Filtration Rate, CNI: Calcineurin Inhibitors.

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Tables

Table 1

Characteristics	Belatacept-treated N=19	CNI-treated N=58	p-value
Age at transplantation, years	36 [9 - 71]	43 [15 - 74]	0.5
Female, n (%)	8 (42.1)	18 (31.0)	0.9
Cause of ESRD, n (%)			
IgA nephropathy	2 (10.5)	17 (29.3)	0.3
Diabetes	0	2 (34.5)	
Nephrosclerosis	2 (10.5)	4 (6.9)	
Other glomerulonephritis	3 (15.8)	4 (6.9)	
Cystic renal disease	2 (10.5)	7 (12.1)	
Tubulointernstitial or uropathy	7 (36.8)	12 (20.7)	
Other	2 (10.5)	2 (34.5)	
Unknown	1 (5.3)	10 (17.2)	
Prior solid organ transplantation, n (%)	3 (15.8)	7 (12.1)	0.7
Donor type, n (%)			
Deceased	17 (89.5)	53 (91.4)	0.8
Induction therapy, n (%)			
Basiliximab	10 (52.6)	26 (44.8)	0.7
Antithymoglobulin	9 (47.4)	32 (55.2)	
CNI type at biopsy, n (%)			
Tacrolimus	13 (68.4)	24 (41.4)	0.08
Ciclosporin	6 (10.3)	29 (50.0)	
mTOR inhibitor, n (%)	0	5 (8.6)	
MFI of immunodominant DSA	4298 ± 3912	4929 ± 5265	0.9
Corticosteroids at biopsy, n (%)	13 (68.4)	27 (46.6)	0.1
Corticosteroids after biopsy, n (%)	12 (63.2)	44 (75.9)	0.3
Anterior cellular rejection, n (%)	6 (31.6)	13 (22.4)	0.4
Previous treatment of active ABMR, n (%)	8 (42.1)	15 (25.9)	0.2
Year of biopsy, n (%)			
Before 2014	10 (52.6)	44 (75.9)	**0.05**
After 2015	9 (47.4)	14 (24.1)	
Time between KT and biopsy, months	80 [12 - 435]	75 [4 - 376]	0.9
eGFR 3 months before biopsy, mL/min/1.73m^2	38.3 ± 19.0	35.7 ± 13.0	0.5
eGFR at biopsy, mL/min/1.73m^2	37.9 ± 17.9	35.7 ± 14.9	0.6
Proteinuria/creatininuria ratio at biopsy, g/g	0.8 ± 1.1	1.3 ± 1.2	0.2
Banff score			
cg	1.6 ± 1.0	1.8 ± 0.8	0.4
ci	1.8 ± 1.0	1.5 ± 0.8	0.2
ct	1.4 ± 0.9	1.0 ± 0.8	0.1
cv	1.1 ± 1.0	1.3 ± 0.9	0.3
mm	0.8 ± 0.8	1.2 ± 0.8	0.8
ptc	1.1 ± 0.8	1.6 ± 0.9	**0.05**
t	0.3 ± 0.7	0.1 ± 0.2	**0.02**
i	0.5 ± 0.6	0.6 ± 0.6	0.5
g	1.5 ± 0.6	1.8 ± 0.6	0.06
ah	1.7 ± 1.3	1.6 ± 1.1	0.6
v	0.1 ± 0.5	0 ± 0	0.08
g + ptc	2.6 ± 0.8	3.4 ± 1.1	**0.007**
i + t	0.7 ± 1.2	0.6 ± 0.7	0.6
ci + ct	3.2 ± 1.8	2.5 ± 1.5	0.1
cv + ah	2.8 ± 1.2	2.9 ± 1.4	0.8
ti	1.4 ± 0.9	1.0 ± 0.9	0.1
i-IFTA	1.8 ± 0.9	1.5 ± 0.8	0.1
Time between biopsy and switch to Belatacept, days	44 [28 - 175]	NA	
Time of follow-up, months	23 [4 - 87]	80 [11 - 125]	0.1

Table 1: characteristics at baseline. Results for quantitative data are median [min – max] and mean ± standard deviation. CNI: Calcineurin Inhibitors, ESRD: End-Stage Renal Disease, MFI: Mean Fluorescence Intensity, DSA: Donor-Specific-Antibody, eGFR: estimated Glomerular Filtration Rate (MDRD), ABMR: Antibody Mediated Rejection, KT: Kidney Transplant, NA: not applicable, IFTA: Interstitial Fibrosis and Tubular Atrophy.

Table 2

Characteristic	Univariate analysis	Multivariate analysis		
	p	HR	95% CI	p
Donor type	0.8	/		
Sex	0.2	/		
Age at the biopsy	0.9	/		
Delay between KT and biopsy	0.8	/		
eGFR at the biopsy	**0.0002**	0.96	[0.94 – 0.99]	**0.04**
Proteinuria/creatininuria ratio at the biopsy	0.06	0.87	[0.68 – 1.13]	0.3
cg score	**0.003**	2.21	[1.37 – 3.55]	**0.01**
cv score	**0.0006**	1.92	[1.24 – 2.96]	**0.03**
ah score	0.4	/		
g + ptc score	0.8	/		
i + t score	0.2	/		
ci + ct score	**0.003**	1.16	[0.90 – 1.50]	0.2
Switch to Belatacept	0.6	/		

Table 2: risk factors for graft loss according to baseline characteristics. HR: Hazard Ratio, CI: confidence interval, KT: Kidney Transplant. eGFR: estimated Glomerular Filtration Rate, cg: transplant glomerulopathy, cv: transplant arteriopathy, ah: arteriolar hyalinosis, g: glomerulitis, ptc: peritubular capillaritis, i: interstitial inflammation, t: tubulitis, ci: interstitial fibrosis, ct: tubular atrophy

Table 3

All cohort	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 5.2 ± 8.6	- 8.8 ± 9.3	- 9.1 ± 14.3
CNI-treated	- 7.1 ± 13.3	- 12.8 ± 13.9	- 18.6 ± 15.1
p value	0.6	0.3	**0.05**
cg score < 2	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 3.8 ± 11.1	- 7.4 ± 11.5	- 5.6 ± 19.3
CNI-treated	- 1.4 ± 9.9	- 6.4 ± 11.0	-9.9 ± 11.1
p value	0.7	0.9	0.5
cg score ≥ 2	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 6.1 ± 7.1	- 9.7 ± 8.3	- 11.6 ± 10.4
CNI-treated	- 9.9 ± 14.1	- 16.0 ± 14.2	- 23.1 ± 15.0
p value	0.5	0.3	**0.06**
CNI toxicity : no	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 3.3 ± 7.8	- 12.8 ± 3.7	- 12.0 ± 0.8
CNI-treated	- 6.3 ± 15.4	- 13.4 ± 17.2	- 21.1 ± 18.0
p value	0.7	0.9	0.3
CNI toxicity : yes	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 6.1 ± 9.2	- 6.8 ± 10.8	- 7.6 ± 17.7
CNI-treated	- 7.9 ± 10.9	- 12.1 ± 9.3	- 15.9 ± 10.8
p value	0.7	0.2	0.1
cv score < 2	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 4.6 ± 9.7	- 9.3 ± 11.1	- 7.3 ± 17.5
CNI-treated	- 3.2 ± 13.3	- 10.2 ± 15.6	- 17.8 ± 17.5
p value	0.8	0.9	0.1
cv score ≥ 2	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 6.3 ± 7.1	- 7.8 ± 5.5	- 12.8 ± 3.3
CNI-treated	-12.0 ± 12.0	- 16.1 ± 10.7	- 19.6 ± 11.6
p value	0.4	0.1	0.3
Baseline eGFR ≥ 35	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	1.3 ± 7.9	- 2.5 ± 12.2	3.3 ± 19.2
CNI-treated	- 10.0 ± 16.4	- 16.4 ± 16.5	- 25.3 ± 17.1
p value	0.2	0.1	**0.005**
Baseline eGFR < 35	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 8.4 ± 7.3	- 11.9 ± 6.3	- 15.3 ± 5.6
CNI-treated	- 4.3 ± 9.2	- 9.4 ± 10.2	- 12.4 ± 9.7
p value	0.3	0.5	0.4

Table 3: delta of eGFR (mL/min/1.73m^2) between 1 year and Day 0, 2 years and Day 0 and 3 years and Day 0, between Belatacept-treated group and CNI-treated group, according to Banff score and baseline eGFR. Differences which reached or trended to statistically significance are highlighted. CNI: Calcineurin Inhibitors, cg: transplant glomerulopathy, cv: transplant vasculopathy, eGFR: estimated Glomerular Filtration Rate.

Figures

Figure 1

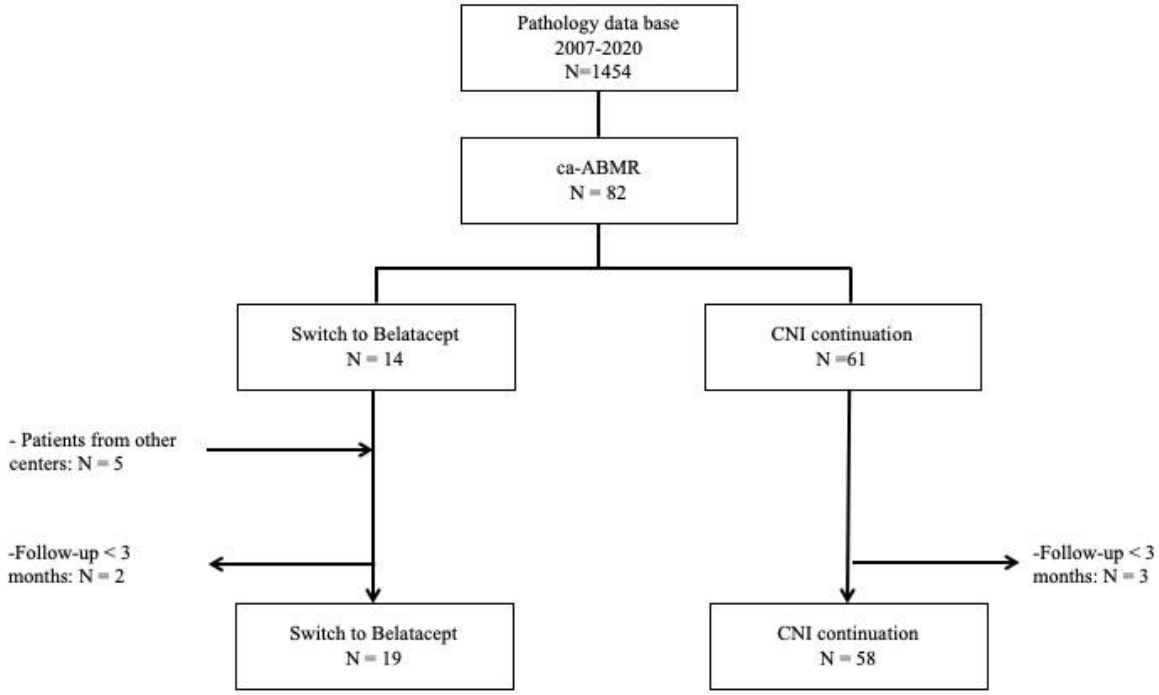
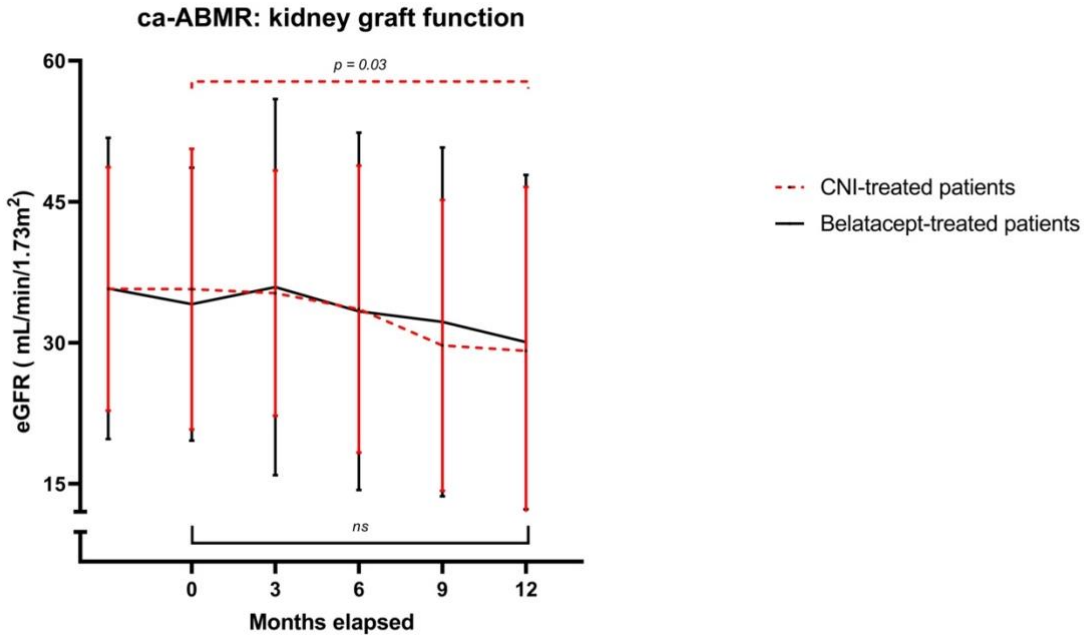


Figure 2


ca-ABMR: kidney graft function
p = 0.03
ns
eGFR (mL/min/1.73m2)
60
45
30
15
0
3
6
9
12
Months elapsed
CNI-treated patients
Belatacept-treated patients

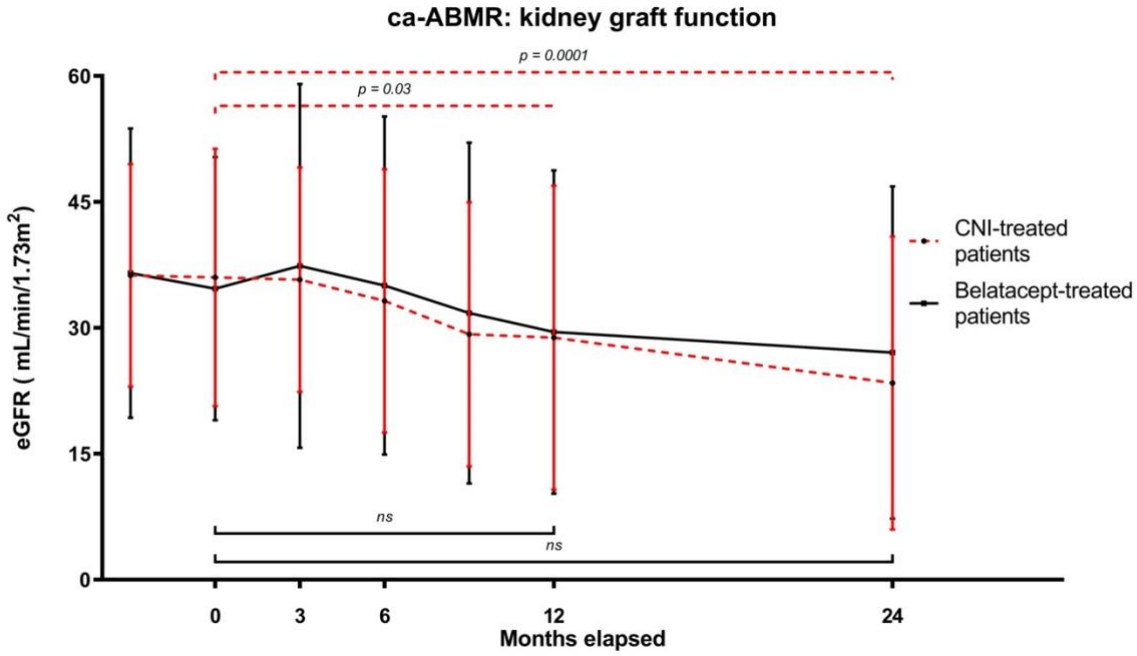
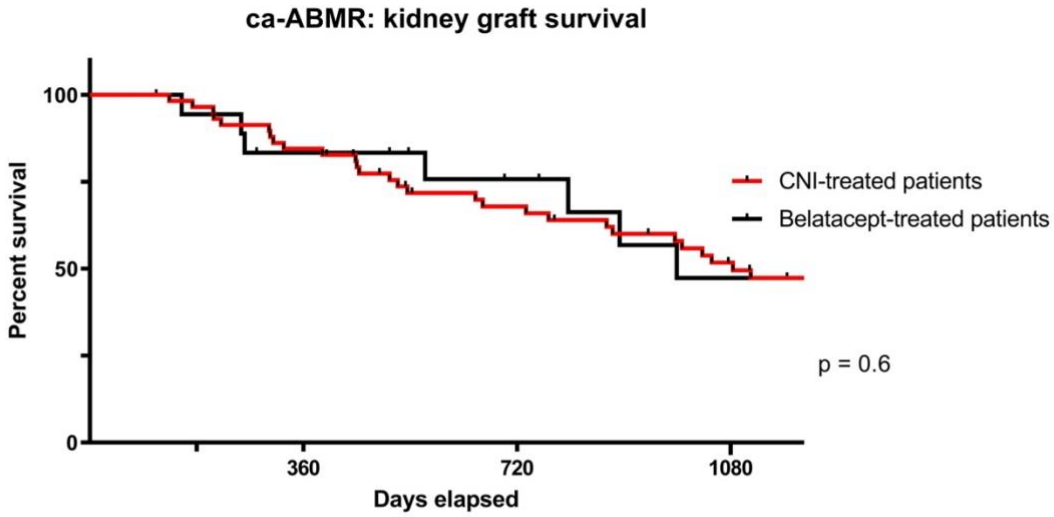
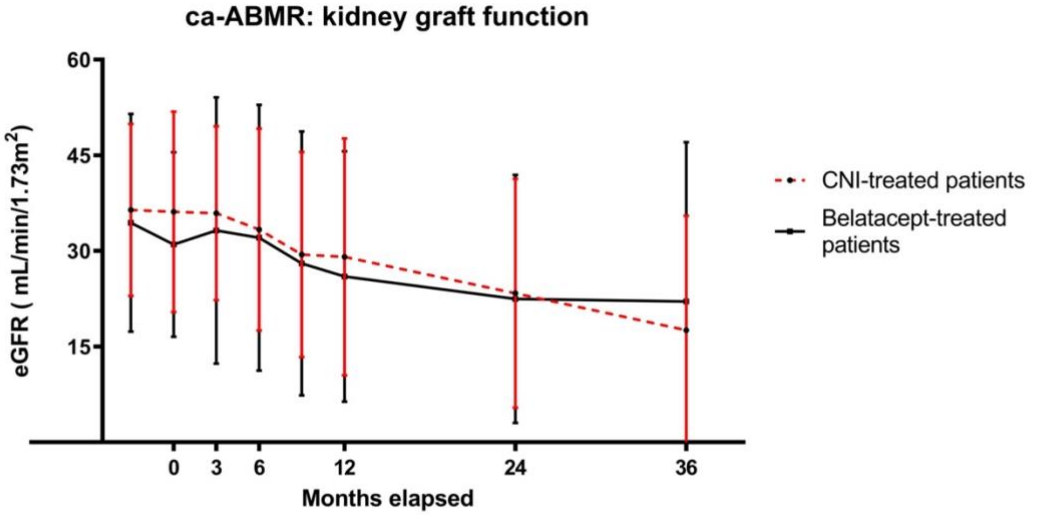

ca-ABMR: kidney graft function
p = 0.0001
p = 0.03
ns
ns
eGFR (mL/min/1.73m2)
60
45
30
15
0
0
3
6
12
24
Months elapsed
CNI-treated patients
Belatacept-treated patients

Figure 3

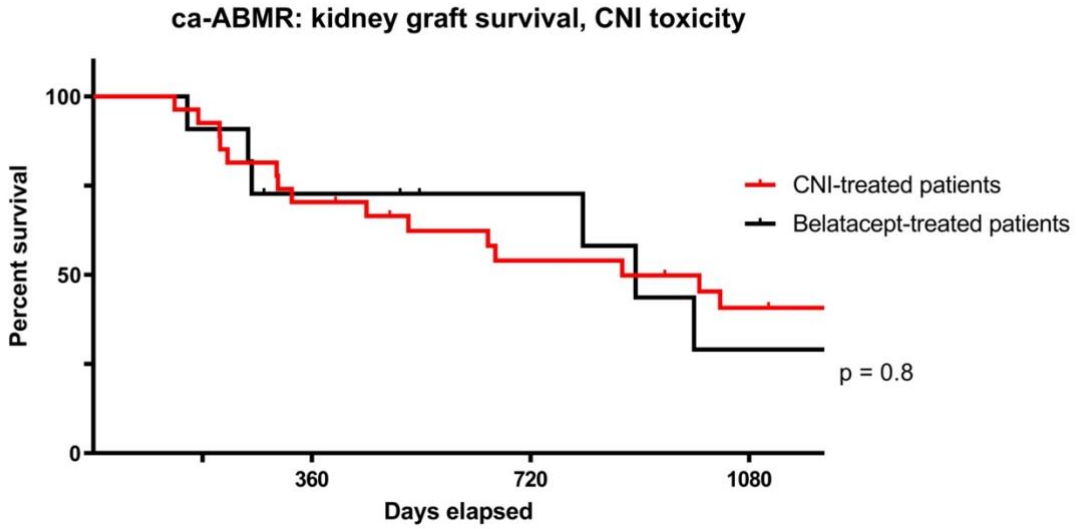


No. of events/No. at risk	Baseline	1 year	2 years	3 years
Belatacept-treated	0/19	3/13	4/10	7/5
CNI-treated	0/58	9/49	18/35	17/24

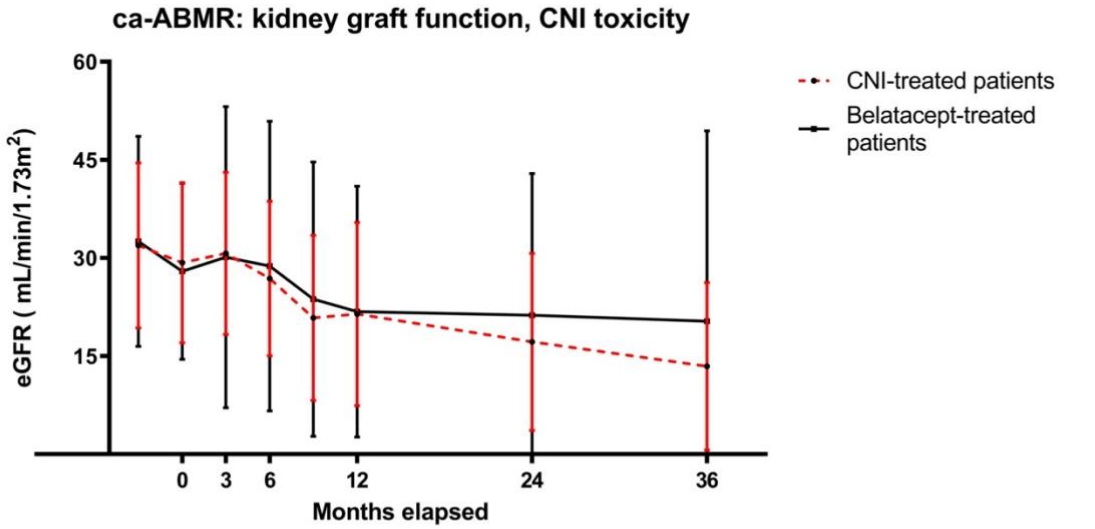


	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 5.1 ± 8.6	- 8.8 ± 9.3	- 9.1 ± 14.3
CNI-treated	- 7.1 ± 13.3	- 12.8 ± 13.9	- 18.6 ± 15.1
p value	0.6	0.3	**0.05**

Figure 4



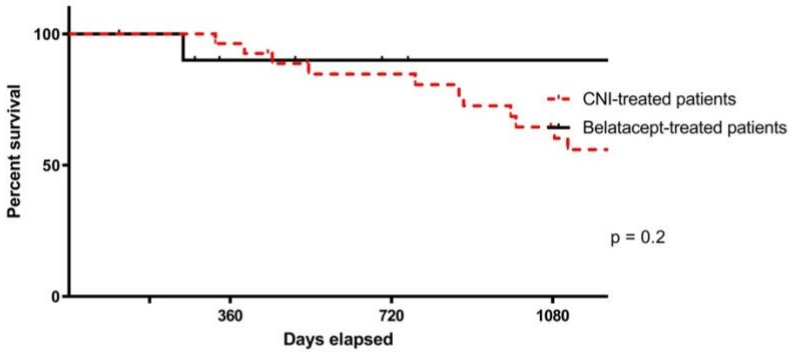
No. of events/No. at risk	Baseline	1 year	2 years	3 years
Belatacept	0/11	3/7	3/5	6/2
CNI	0/27	8/19	12/13	15/9



	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 6.1 ± 9.2	- 6.8 ± 10.8	- 7.6 ± 17.7
CNI-treated	- 7.9 ± 10.9	- 12.1 ± 9.3	- 15.9 ± 10.8
p value	0.7	0.2	0.1

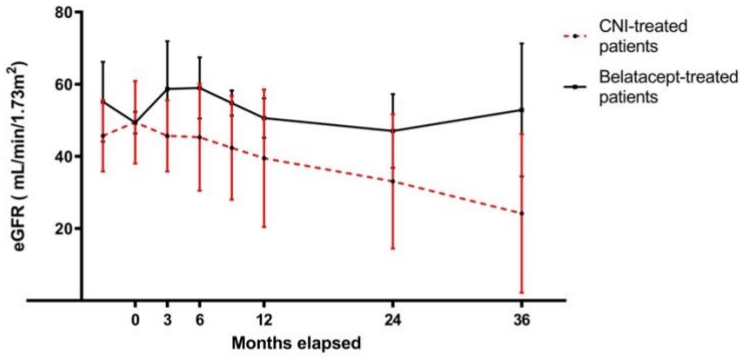
Figure 5

ca-ABMR: kidney graft survival, baseline eGFR ≥ 35 mL/min/1.73m²



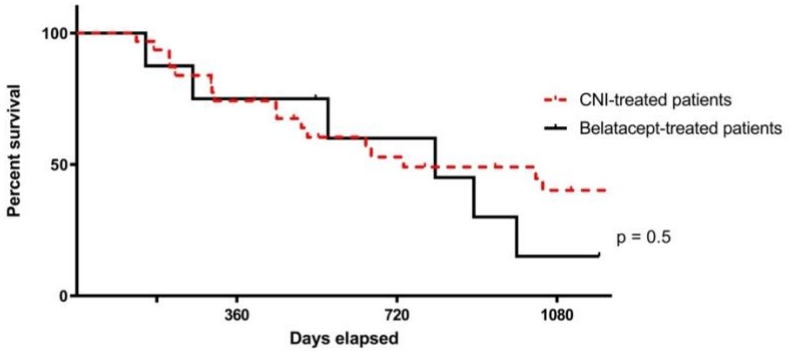
No. of events/No. at risk	Baseline	1 year	2 years	3 years
Belatacept-treated	0/11	1/7	1/6	1/4
CNI-treated	0/27	1/26	4/21	10/15

ca-ABMR: kidney graft function, baseline eGFR ≥ 35 mL/min/1.73m²



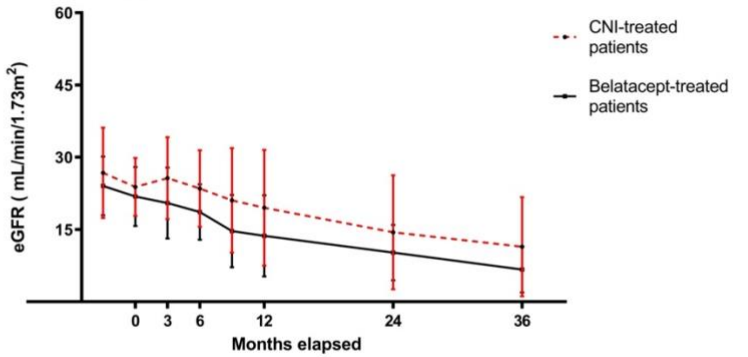
	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	1.3 ± 7.9	- 2.5 ± 12.2	3.3 ± 19.2
CNI-treated	- 10.0 ± 16.4	- 16.4 ± 16.5	- 25.3 ± 17.1
p value	0.2	0.1	**0.005**

ca-ABMR: kidney graft survival, baseline eGFR < 35 mL/min/1.73m²



No. of events/No. at risk	Baseline	1 year	2 years	3 years
Belatacept-treated	0/8	2/6	3/4	6/1
CNI-treated	0/31	8/23	14/14	17/9

ca-ABMR: kidney graft function, baseline eGFR < 35 mL/min/1.73m²



	Delta 1 year – Day 0	Delta 2 years – Day 0	Delta 3 years – Day 0
Belatacept-treated	- 8.4 ± 7.3	- 11.9 ± 6.3	- 15.3 ± 5.6
CNI-treated	- 4.3 ± 9.2	- 9.4 ± 10.2	- 12.4 ± 9.7
p value	0.3	0.5	0.4

Switch from Calcineurin Inhibitors to Belatacept in Kidney Transplant patients with chronic-active Antibody Mediated Rejection results in a lower decline in Kidney Transplant function at three years.

Introduction:
Chronic-active Antibody Mediated Rejection (ca-ABMR) in Kidney Transplant (KT) lacks effective treatment. Hence, latest guidelines recommend usual nephroprotective therapies in which limiting nephrotoxicity is paramount. Belatacept which usefulness in Extended Criteria Donors and chronic vascular changes has been shown could be an interesting alternative to Calcineurin Inhibitors (CNI). This study aims to evaluate if switch from CNI to Belatacept is beneficial on KT survival and function in ca-ABMR.

Methods:
Patients with the diagnosis of ca-ABMR and switched to Belatacept between 2012 and 2020 in four French KT centers were retrospectively included.

Results:
Nineteen patients were switched from CNI to Belatacept and compared to 58 controls with a median follow-up of 29 [4 - 125] months. Biopsy was performed 78 [4 - 140] months after KT, with a mean estimated Glomerular Filtration Rate (eGFR) of 36.2 ± 15.6 mL/min/1.73m^2.
There was no difference of eGFR at baseline, one, two and three years: 31.2 ± 14.5, 26.0 ± 19.7, 22.4 ± 19.5 and 22.1 ± 24.9 mL/min/1.73m^2, respectively, in the Belatacept-treated group, versus 36.1 ± 15.7, 29.1 ± 18.6, 23.4 ± 18.0 and 17.5 ± 18.0 mL/min/1.73m^2 in the CNI-treated group. The delta of eGFR between 3 years and Day 0 was -9.1 ± 14.3 mL/min/1.73m^2 in the Belatacept-treated group versus -18.6 ± 15.1 mL/min/1.73m^2, p = 0.05. This difference was increased when focusing on the subgroup with a baseline eGFR ≥ 35 mL/min/1.73m^2: 3.3 ± 19.2 versus -25.3 ± 17.1 mL/min/1.73m^2, p = 0.005. However, death-censored survival was similar in the two groups at one, two and three years: 81.3%, 71.4% and 41.6%, respectively, in the Belatacept-treated group, versus 84.4%, 66.0% and 47.1%, p = 0.6.

Conclusion:
Switch from CNI to Belatacept may lower decline of eGFR at three years, especially when it is started at an early stage. However, it does not appear to have an effect on death-censored KT survival.

Keywords:
Chronic-active Antibody Mediated Rejection; Belatacept; Kidney Transplant; Chronic Allograft Nephropathy; Immunosuppressive agent;