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Anti-BAFF treatment modulates intragraft fibrosis and DKK3 expression in a non-adherence model of experimental kidney transplantation

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ABSTRACT

Following kidney transplantation, rejection and the presence of interstitial fibrosis and tubular atrophy represent prognostically unfavorable factors and are associated with reduced graft survival. The B-cell activating factor (BAFF) and the profibrotic glycoprotein Dickkopf 3 (DKK3) have been suggested as potential biomarkers and therapeutic targets.

In our rat model, we hypothesized that anti-BAFF treatment could not only influence cellular migration patterns but also mediate intragraft fibrosis and modulate DKK3 expression.

In an allogeneic setting, kidneys of Brown Norway rats were transplanted into Lewis rats with cyclosporine A (CyA) as standard immunosuppressive therapy (highCNI). To permit chronic rejection and the development of donor-specific antibodies (DSA), some rats received a reduced dosage of cyclosporine A (lowCNI), while another group additionally received a monoclonal anti-BAFF antibody (lowCNI+anti-BAFF) to mitigate immunological activation.

The highCNI group exhibited the least immune cell infiltration (CD3/20/68) and lower fibrosis, despite a tendency toward higher DKK3 mRNA levels on day 28. The lowCNI group showed the highest cellular infiltration, accompanied by the most severe fibrosis and a trend toward increased DKK3 expression. In contrast, the lowCNI+anti-BAFF group demonstrated reduced B-cell infiltration, mild fibrosis, and low DKK3 expression.

Thus, the results indicate that the addition of anti-BAFF treatment, can eliminate the detrimental effects of under- and over-immunosuppression.

1. Introduction

In end-stage kidney disease (ESKD), kidney transplantation is the kidney replacement therapy offering the best over-all morbidity and mortality compared with the alternative of patients remaining on dialysis [1]. Kidney transplant survival is significantly limited by rejection-mediated inflammatory processes leading to allograft fibrosis [2–4].

Interstitial fibrosis and tubular atrophy (IFTA) represent the final common histopathologic outcome of various kidney diseases, marking the end-stage of a complex interrelated cascade of cellular damage and repair mechanisms. [5–8].

In a clinical context, IFTA is a strong predictor of poor prognosis in chronic kidney disease (CKD) and in renal allografts, particularly when accompanied by evidence of inflammation [9]. It is found in more than 25% of the 1-year-surveillance biopsies of renal allografts despite concurrent stable renal function. [10]

B-cell activating factor (BAFF), which is secreted by hematopoetic cells, is a member of the TNF protein family and plays an important role in B-cell development and survival.

Elevated levels of BAFF have been found in patients with systemic lupus erythematodes (SLE) and have been associated with increased disease activity [11,12].

BAFF not only affects B-cell maturation and survival, its receptor has also been identified on the surface of Th17-cells [13].

In both SLE and lupus nephritis (LN), the anti-BAFF antibody Belimumab has been approved for treatment and has gained therapeutic significance in recent years. It has been shown to slow eGFR decline and progression of albuminuria in biopsy-proven LN [14,15], while histological evidence of reduced IFTA is lacking.

In transplantation, BAFF levels have also been shown to correlate

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with patients'individual immunological risk of de novo HLA antibody formation [16], rejection [17], in particular antibody-mediated rejection (ABMR) [18,19], and have been used as a tool for stratification of immunological risk profiles [20]. Anti-BAFF treatment has been shown to reduce the risk of ABMR in rats in a chronic rejection model [21] and has been used in highly immunocompromized dialysis patients awaiting kidney transplantation to lower their cPRA [22]. It has also been used in a phase 2 trial for induction and maintenance therapy [23].

Dickkopf-3 (DKK3) is a member of the Dickkopf glycoprotein family consisting of 4 members (DKK 1–4), which has been shown to be an immune modulator influencing the local T-cell response and a promoter of renal fibrosis via the WNT/β-catenin pathway [24,25]. The fact that genetic or pharmaceutical inhibition of DKK3 decreases renal fibrosis in those models makes it a potential therapeutic target.

We hypothesized that add-on anti-BAFF treatment might specifically affect cellular migration patterns. In addition, we asked whether this might translate into mediation of intragraft fibrosis and whether this might be reflected in differentiated DKK3 expression profiles.

2. Methods & materials

2.1. Animal models and experimental treatments

Animal experiments were approved by local authorities (Regierung von Unterfranken, 55.2–2532-2-47) and performed according to animal protection laws.

Renal transplantation (RTx) was performed as previously described [26]. Male Brown Norway (BN) rats served as donors and male Lewis (LEW) rats as recipients (Charles River Laboratories, Sulzfeld, Germany). Left BN kidneys were transplanted orthotopically into LEW rats. All rats (Charles River Laboratories, Sulzfeld, Germany) were male, weighing 200–225 g, and kept under conventional housing and diet. The number and the treatment regimens of the different groups are listed in Table 1. Standard immunosuppression was 10 mg/kg/day cyclosporine A (highCNI, $n = 10$) (Neoral, Novartis, Basel, Switzerland) administered once daily by gavage. In contrast, some rats received reduced doses of cyclosporine A (5 mg/kg/day) on d0–d7 post-RTx, followed by administration on alternating days from d7 onward (lowCNI, $n = 10$). Measured trough levels between both groups were significantly different. Another group (total $n = 9$) received, in addition to the low dose cyclosporine A treatment, a monoclonal anti-BAFF antibody (hamster anti-mouse BLYS antibody, provided by GSK) at 10 mg/kg/day (lowCNI+anti-BAFF) intraperitoneally on days 3, 17, 31 and 45 post-RTx as published previously [27]. Half of the rats of every experimental group were euthanized on d28, the other half on d56 post-RTx. Transplantation was performed as published earlier: male (BN) rats served as donors and male LEW rats as recipients. The left kidneys were explanted from BN donors, flushed with cold saline and transplanted orthotopically into LEW recipient rats by end-to-end anastomosis of the vessels followed by anastomosis of the donor and recipient ureters. Cold and warm ischemia times were approximately 35 and 30 min, respectively. Nephrectomy of the right recipient (LEW) kidney was performed at the end of surgery. As an additional control for the effect of allogeneic transplantation, syngeneic transplantation (LEW-LEW) was performed as a control without the use of any immunosuppressive agents and euthanized on day 56 ($n = 5$). An overview of the experimental groups is depicted in Table 1.

Table 1
Overview of the different treatment groups within the renal transplantation rat model.

	Group	Treatment	Treatment duration	Group size
Allogeneic	highCNI	CyA (10 mg/kg/d) daily	28 days	n = 5
			56 days	n = 5
	lowCNI	CyA (5 mg/kg/d) on alternate days	28 days	n = 5
			56 days	n = 5
	lowCNI+aBAFF	CyA (5 mg/kg/d) on alternate days + anti-BAFF-antibody (10 mg/kg i.p.) days 3,17,31,45	28 days	n = 5
			56 days	$n = 4$
Syngeneic	syngen	syngeneic transplant with no immunosuppressive treatment	56 days	n = 5

2.2. Histology and immunohistochemistry

Harvested allografts were formalin-fixed and paraffin-embedded (FFPE), sectioned and subsequently stained with hematoxylin/eosin and periodic acid-Schiff. Morphology was evaluated histologically by an independent nephropathologist in accordance with criteria comparable to the Banff classification [28].

FFPE sections of 3 μm thickness were stained with polyclonal rabbit anti-DKK3 IgG (Invitrogen, PA5–102626), monoclonal rabbit anti-CD68 IgG (Serotec, MCA341GA), polyclonal rabbit anti-CD3 IgG (Abcam, ab5690), monoclonal rabbit anti-CD4 IgG (CellSignaling 25, 229-S), monoclonal mouse anti-CD8 IgG (Santa Cruz sc-70, 802), monoclonal rabbit anti-CD20 IgG (Abcam ab64088) and monoclonal mouse anti-alpha-SMA (Agilent Dako, M0851). Staining was performed according to a standard immunohistochemistry protocol [29].

Additional Masson's trichrome staining was performed according to standard procedure for histologic evaluation of fibrosis.

These stains were used to evaluate the number of T-lymphocytes (CD3+, CD4+, CD8+), macrophages (CD68+) and B-cells (CD20+). Their numbers were then calculated as a percentage of the total number of nucleated cells in each kidney section. Alpha-SMA and trichrome-positive area was calculated as a percentage of the total area analyzed. Histological analysis was performed automatedly using HistoQuest (TissueGnostics) on whole slides captured with a Zeiss Axiostar microscope at 20× magnification.

Increased expression of alpha-SMA by myofibroblasts is one of the key findings in the ongoing excessive deposition of extracellular matrix components such as collagen and fibronectin [30].

2.3. Real-time PCR

Quantitative polymerase chain reaction (qPCR) was performed as previously described [37]. The sequences of the primers are

rHPRTneu for: 5′-GCA GAC TTT GCT TTC CTT GG-3′
rHPRTneu rev: 5′-TCC ACT TTC GCT GAT GAC AC-3′
rDKK3 forw1: 5′-AAG GCA AGA AGA GCC ATG AA-3′
rDKK3 rev1: 5′-CTC ACT GTC TCG GGT GCA TA-3′

Copy numbers of target genes were normalized to the expression of house-keeping gene hypoxanthine-guanine phosphoribosyltransferase (HPRT) and shown as delta cycle threshold values.

2.4. Statistical analysis

Data was analyzed using IBM SPSS Statistics (version 25). Since multiple of the examined variables were not normally distributed, a nonparametric test was chosen. Kruskal-Wallis H tests were used to compare outcomes between groups. Tests were conducted in an exploratory manner. No adjustments for multiple comparisons were made.

3. Results

3.1. Anti-BAFF treatment prevents development of chronic rejection caused by underimmunosupression

On day 28, the proportion of CD20-positive B-cells in the kidney grafts was significantly lower in the highCNI group than in the lowCNI group (median 0.04%, 95% CI: 0.012–0.068, IQR 0.02–0.06 vs. median 0.34%, 95% CI: 0.069–1.17, IQR 0.19–1.02; $p = 0.003$).

The lowCNI animals receveing anti-BAFF therapy showed also a reduced infiltration of CD20-positive B-cells. However, when compared to the lowCNI group, the significance level was not reached (Fig. 1).

These results were also confirmed on day 56. Here, too, the lowCNI group showed the most pronounced infiltration of CD20-positive B cells both compared with high CNI (median 0.13%, 95% CI: 0.016–0.44, IQR 0.11–0.39 vs. median 0.02%, 95% CI: 0.0058–0.038, IQR 0.01–0.035; $p = 0.018$) and lowCNI+aBAFF (median 0.02%, 95% CI: 0.0095–0.026, IQR 0.013–0.02; $p = 0.013$) (Fig. 1).

In contrast, lowCNI rats receiving anti-BAFF therapy had CD20-positive B-cell counts comparable to those in high-CNI transplanted kidneys (Fig. 1).

3.2. Anti-BAFF therapy reduces T-cell infiltration only after 56d

Since the results for the various T-cell markers (CD4, CD8, CD3) were nearly identical, the results for the pan-T-cell marker CD3 (Fig. 2) are presented as representative of all analyses.

On day 28, significantly fewer CD3+ T-cells were detected in the highCNI group than in lowCNI (median 0.61%, 95% CI:0.22–1.10, IQR 0.37–0.97 vs. median 2.87%, 95% CI 0.31–5.43, IQR 1.14–4.60; $p = 0.04$).The comparison between the highCNI group and the lowCNI+anti-BAFF group also showed a statistically significant difference with higher values in the lowCNI+anti-BAFF group (median 3.06%, 95% CI: 2.41–4.23, IQR 2.79–3.99; $p = 0.002$). On day 56, the difference between the highCNI and lowCNI group remained statistically significant (median 0.4%, 95% CI: 0.65–0.73, IQR 0.17–0.63 vs. median 1.95%, 95% CI: 0.98–2.76, IQR 1.15–2.55; $p = 0.005$), whereas the difference between highCNI and lowCNI+anti-BAFF (median 0.59%, 95% CI: 0.20–0.95, IQR 0.34–0.80; $p = 0.47$) no longer reached statistical significance (Fig. 2).

3.3. Anti-BAFF therapy reduces macrophage infiltration only after 56d

The results of macrophage staining (CD68) are comparable to those of the T cell analysis.

On day 28, the highCNI group exhibited significantly lower values than the lowCNI (median 1.09%, 95% CI 0.58–1.47, IQR 0.69–1.35 vs. median 2.54%, 95% CI: 1.46–3.15, IQR 1.67–2.82; $p = 0.048$) and lowCNI+anti-BAFF (median 2.89%, 95% CI 1.12–3.74, IQR 1.32–3.30; $p = 0.024$).

On day 56, the highCNI group continued to show lower values than the other two groups, but the difference was statistically significant only when compared to the lowCNI group (median 0.32%, 95% CI: 0.026–0.96 vs. 2.10%, 95% CI: 0.84–3.23, IQR 1.14–2.91; $p = 0.013$) (Fig. 3).

However, the group with lowCNI and anti-BAFF therapy (median 0.62%, 95% CI: 0.11–1.23, IQR 0.36–1.04; $p = 0.118$) showed a trend toward a lower cell infiltration compared to the lowCNI group (Fig. 3).

3.4. Anti-BAFF only slightly reduces fibrosis compared to high-dose CyA

Neither on day 28 nor on day 56 the trichrome positive area did not differ significantly between any of the groups, with all groups showing approximately 1% trichrome positive area.

On day 56, although the difference did not reach statistical significance, the lowCNI + anti-BAFF group exhibited a trend toward reduced trichrome-positive areas compared to the lowCNI group, but with levels still higher than those observed in the highCNI group (Fig. 4).

These findings were further supported by the results of the alpha-SMA staining.

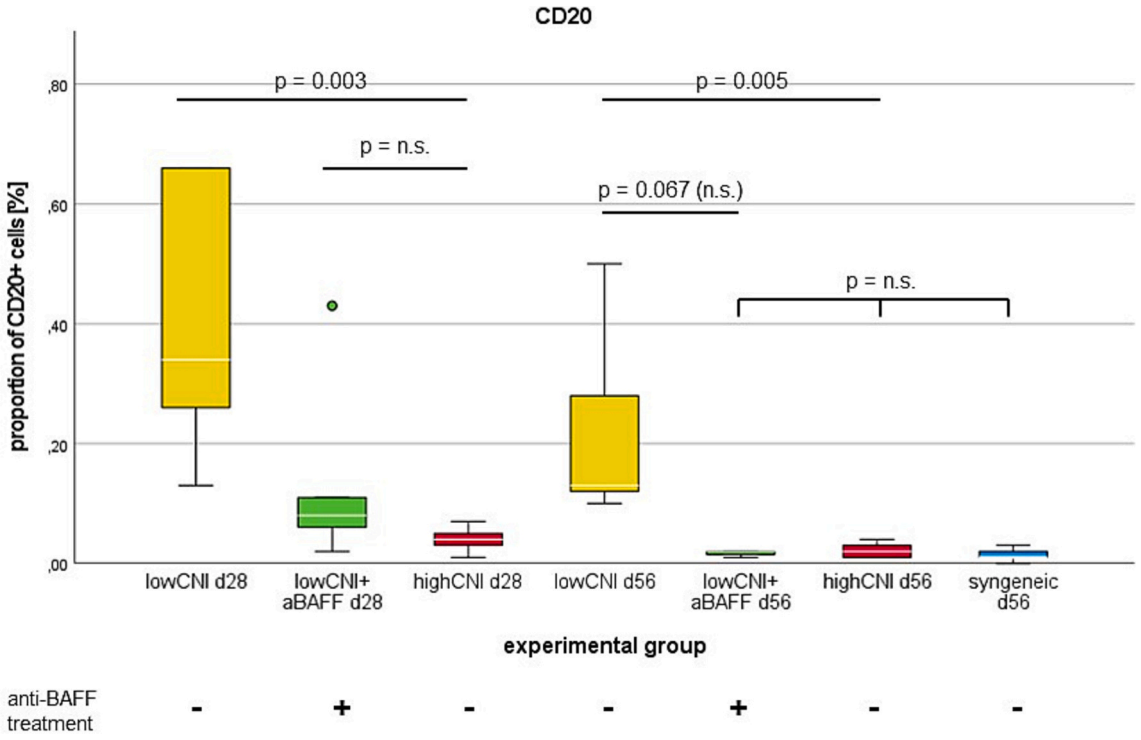

Fig. 1. Boxplot showing the percentage of CD20-positive B-cells in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy, and in syngeneically transplanted controls.

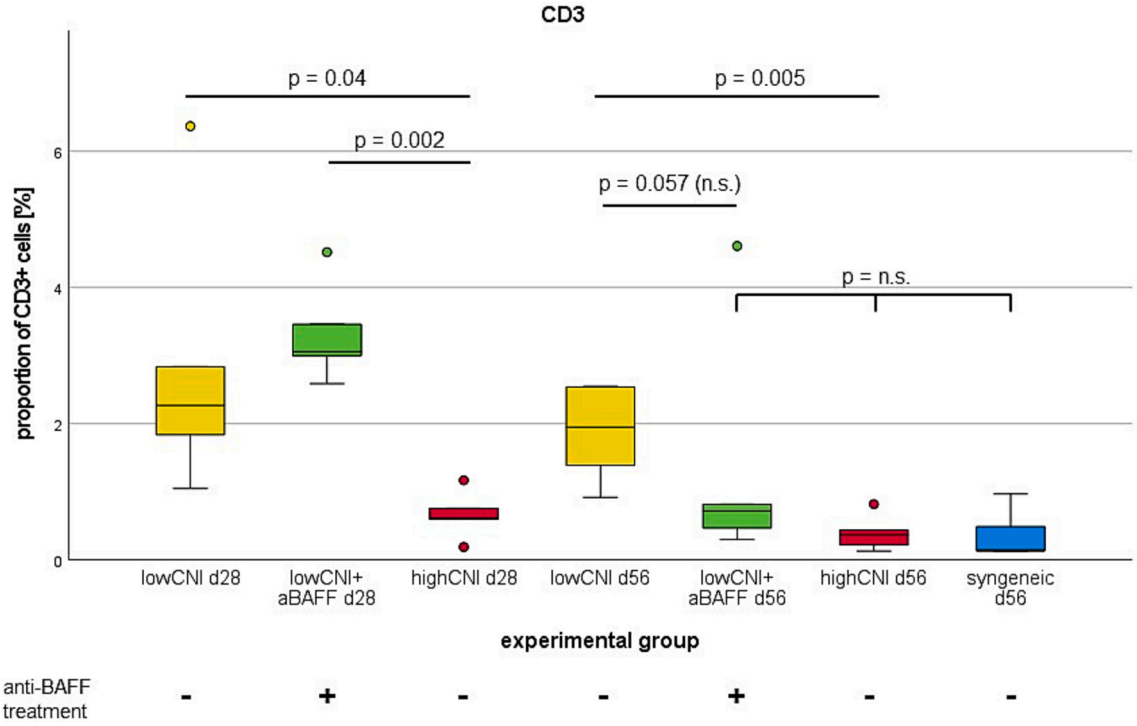

Fig. 2. Boxplot showing the percentage of CD3-positive T-cells in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy, and in syngeneically transplanted controls.

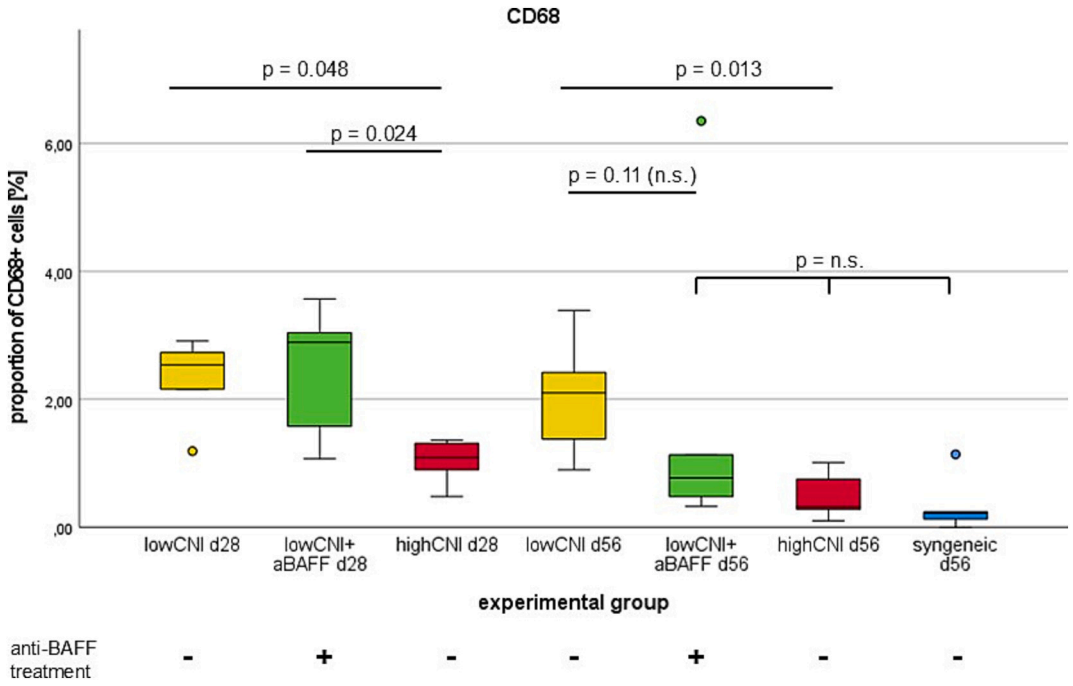

Fig. 3. Boxplot showing the percentage of CD68-positive macrophages in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy, and in syngeneically transplanted controls.

On day 56, the lowCNI group again demonstrated the highest amount of alpha-SMA-positive area compared to both highCNI (median 5.74%, 95% CI: 4.46–7.07, IQR 4.92–6.66 vs.median 2.05, 95% CI: 0.07–4.37, IQR 0.79–3.73; $p = 0.004$) and lowCNI+anti-BAFF (median 2.97%, 95% CI: 1.81–4.34, IQR 2.36–3.88; $p = 0.048$) (Fig. 5).

3.5. DKK3 expression on protein and gene level was elevated in high-dose CyA treated mice

Immunohistochemistry was performed to assess DKK3 protein expression. Quantification of the DKK3-positive area within the

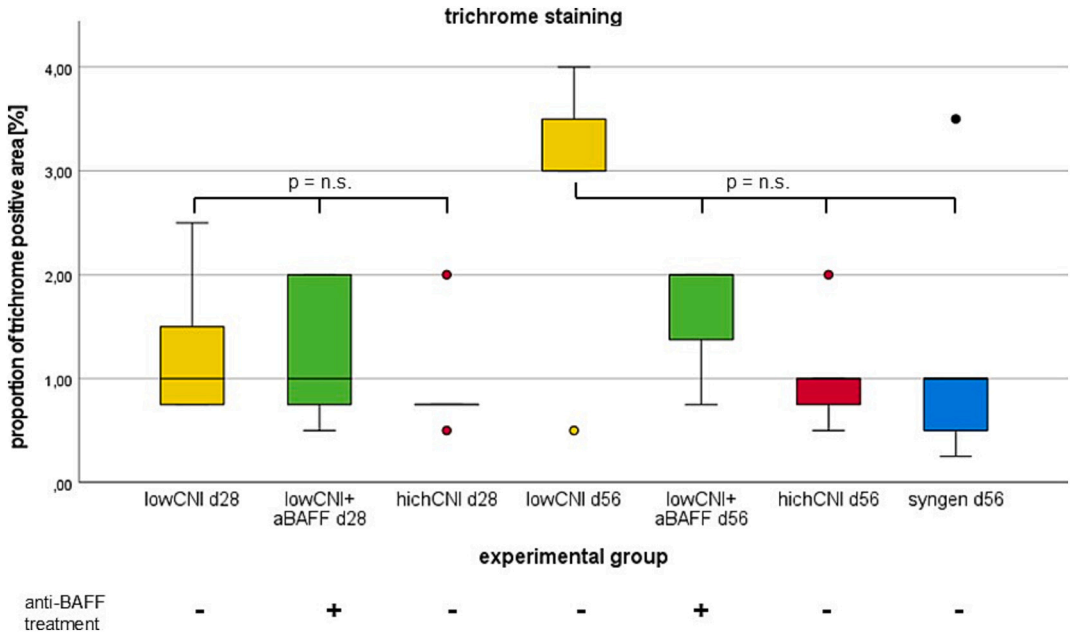

Fig. 4. Boxplot showing the percentage of trichrome-positive area in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy, and in syngeneically transplanted controls.

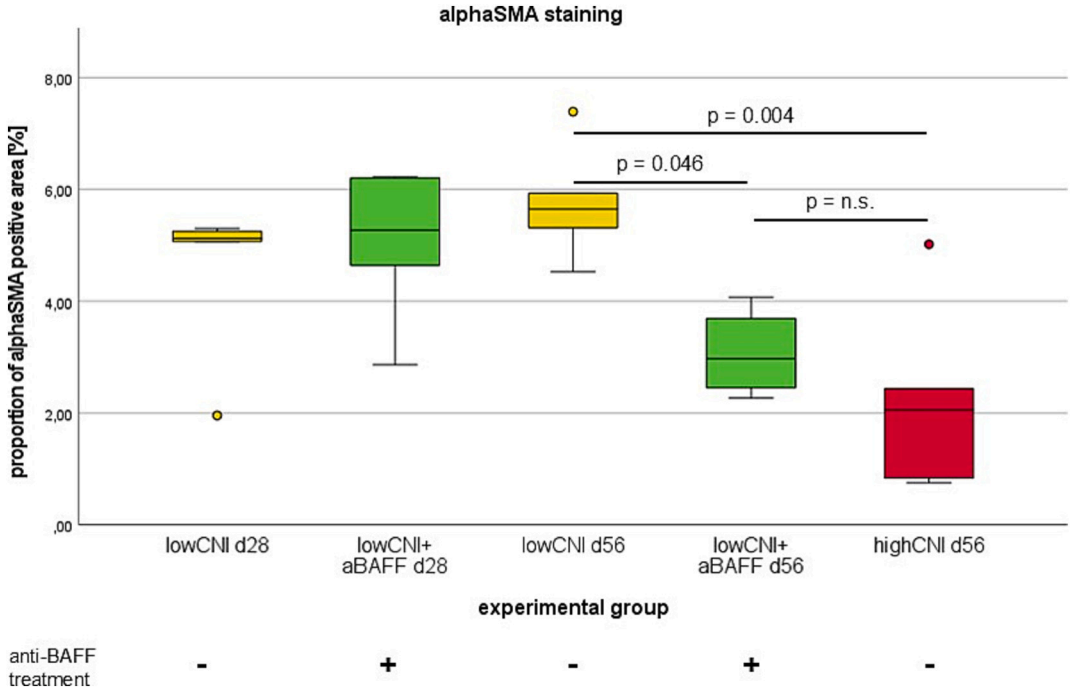

Fig. 5. Boxplot showing the percentage of αSMA-positive area in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy.

histological samples was performed both manually and automatically (HistoQuest, TissueGnostics) (Fig. 6).

On day 28, highCNI treated rats exhibited the highest mean DKK3 positive area with minimal variance, although no statistically significant differences were observed compared to other groups at either time point. The lowCNI and lowCNI+antiBAFF groups, on the other hand, showed similarly low mean DKK3 positive areas (Fig. 7).

To validate these findings, we quantified DKK3 mRNA expression by qPCR, normalizing results to the housekeeper gene hypoxanthine-guanine phosphoribosyltransferase.

Consistently low DKK3 mRNA levels were observed in the low-CNI+anti-BAFF group on both day 28 and day 56.

Although highCNI and lowCNI groups demonstrated a trend toward higher DKK3 mRNA concentrations on day 56, these differences did not reach statistical significance (Fig. 8).

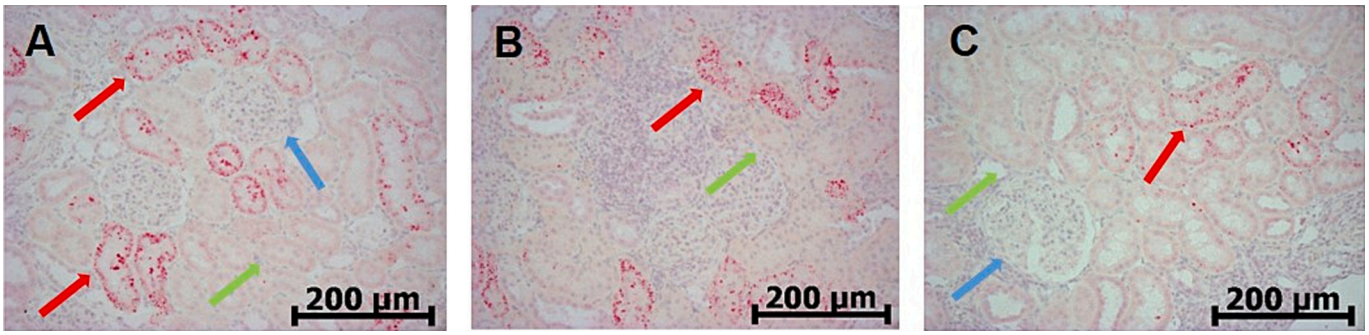

Fig. 6. Representative immunohistochemical staining of DKK3 (Invitrogen, PA5–102626, 1:200 dilution) in FFPE sections of kidney grafts from the rat transplant model in a 20fold magnification. Examples depict the different treatment groups of highCNI (A), lowCNI (B) and lowCNI+anti-BAFF (C) on day 28. Key structural features are indicated by colored arrows: preserved proximal tubules (green), glomeruli (blue), and DKK3-expressing tubules (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

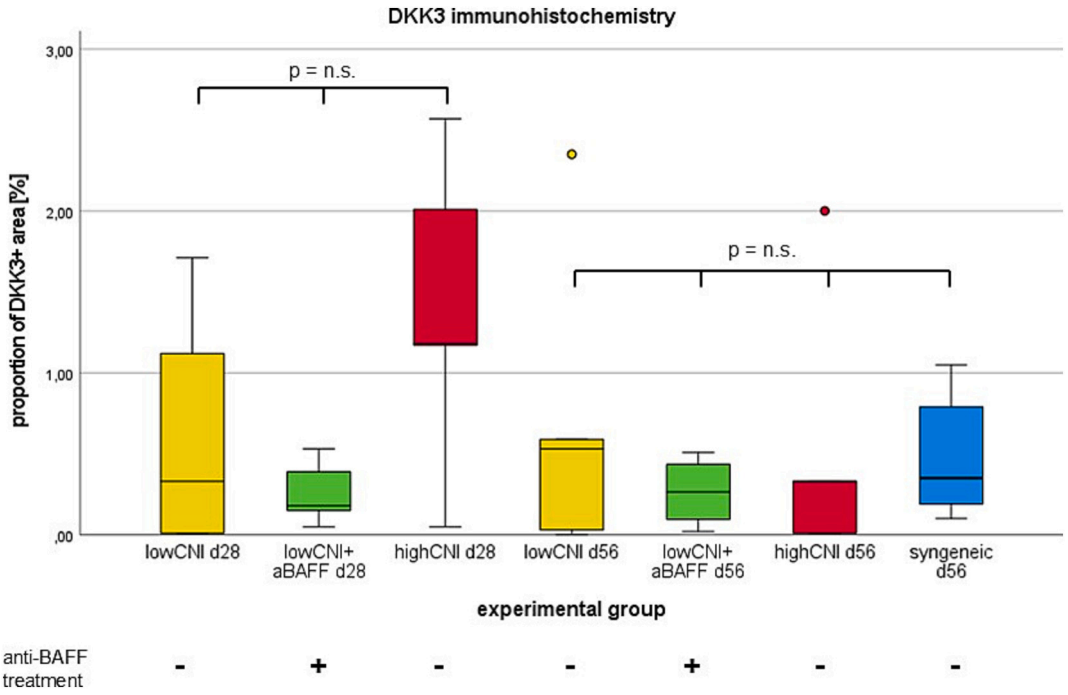

Fig. 7. Boxplot showing the percentage of DKK3-positive area in cross-sections of transplanted rat kidneys. Immunohistochemical analysis was performed on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy, and in syngeneically transplanted controls.

4. Discussion

In summary, our rat transplant model was designed to investigate both the effect of reduced and intermittent calcineurin inhibitor (CNI) dosing and the additional impact of pharmacological B-cell intervention on immune cell infiltration, intragraft fibrosis and DKK3 expression in an exploratory manner.

This model, which simulates patient non-adherence to immunosuppressive regimens, previously demonstrated increased formation of de novo DSA in the non-adherence group [31]. In our work, we were able to show that administration of higher levels of immunosuppression (highCNI) prevents the infiltration of inflammatory cells, particularly T-cells and macrophages, which are key mediators in the cascade leading to renal fibrosis [32]. The additional administration of an anti-BAFF antibody also shows a trend toward reduced cell immigration on day 56 in lowCNI-treated rats.

In contrast to this observation, however, the group with highCNI showed a trend toward increased DKK3 expression compared to the other two groups.

Previous studies in MHC-mismatched rat kidney transplantation models have shown that lower Cyclosporine A (CyA) doses enhance lymphocyte infiltration and upregulate chemokines such as BAFF and BAFF-receptor [31].

A study of human kidney biopsies from patients suffering from lupus nephritis (LN), showed markedly increased tubulointerstitial BAFF expression in $CD20^{+}$ inflammatory infiltrates [33]. Similarly, in a study of murine LN, BAFF inhibition also attenuated glomerular T-cell infiltration as well as the formation of tertiary lymphoid structures [34]. Analogously, in our study, the addition of anti-BAFF therapy to low-dose CNI immunosuppression resulted in reduced B-cell and T-cell infiltration. These findings demonstrate that anti-BAFF treatment seems to influence the cellular migration pattern of all investigated inflammatory cell populations.

Using trichrome staining and alpha-SMA analysis, we were able to demonstrate that the addition of anti-BAFF therapy was associated with reduced intragraft fibrosis compared to the lowCNI group alone, with

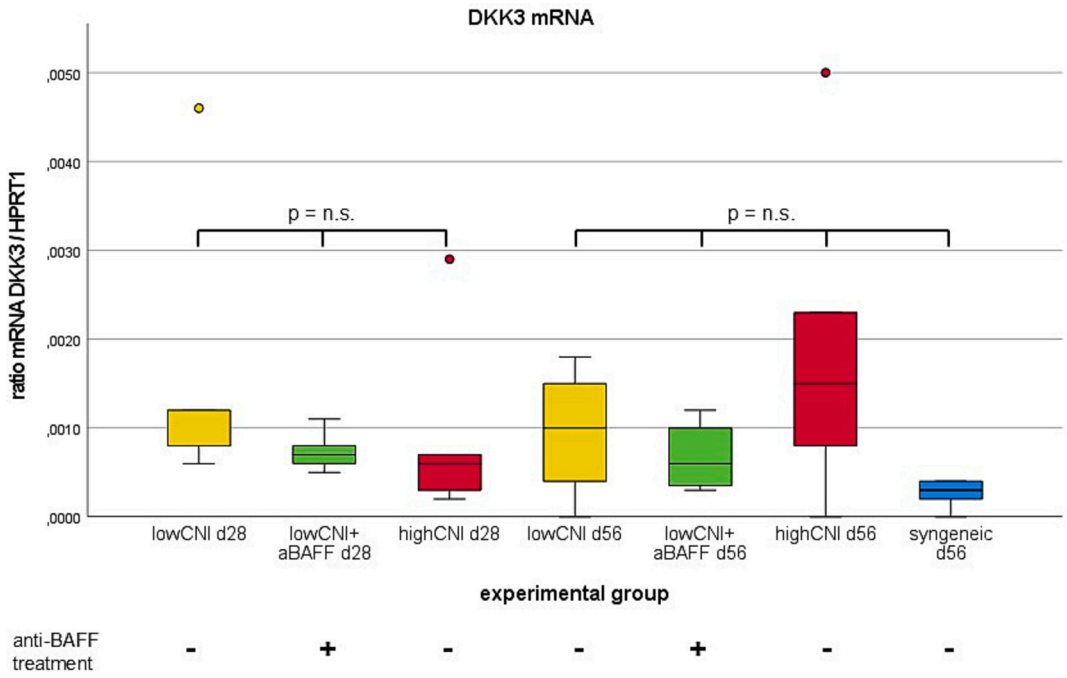

Fig. 8. Box plot showing DKK3 mRNA expression in the kidney grafts from the rat transplant model. DKK3 mRNA expression was measured on days 28 and 56 post-transplantation in animals treated with high-dose CNI (highCNI), low-dose CNI (lowCNI), lowCNI combined with anti-BAFF therapy using quantitative PCR and normalization to the housekeeping gene HPRT1.

the anti-BAFF group exhibiting similarly low fibrosis levels as the highCNI treatment group on day 56.

Evidence from previous studies supports the role of BAFF in (pro-) fibrotic processes: Belimumab (anti-BAFF-antibody) has been shown to suppress fibrosis-associated pathways in patients with systemic sclerosis, particularly TGF-β signaling and syndecan-1, which is also known to activate the profibrotic wnt/β-catenin signaling pathway [35,36], which is also known to be influenced by DKK3.

Although the difference in DKK3 expression between groups did not reach statistical significance, there was a trend toward lower DKK3 expression in the lowCNI+anti-BAFF group on both day 28 and day 56, mirroring the pattern of B-cell infiltration.

Ludwig et al. demonstrated in a mouse model that DKK3 deficiency impairs B2-cell proliferation while enhancing the survival and proliferation of B1-cells, indicating a role of DKK3 in modulating B-cell immune response [37]. Furthermore, Labes et al. showed in a mouse model that administration of 80 mg/kg/d cyclosporine A for four and eight weeks resulted in significantly increased DKK3 mRNA expression, which they interpreted as a possible marker of CyA-induced kidney injury [38]. In our study, animals treated with highCNI (10 mg/kg body weight) also exhibited a trend toward higher DKK3 expression as demonstrated by gene and protein analysis. However, the cyclosporine A doses used in the study of Labes et al. were significantly higher than in our study and we could not detect increased fibrosis in our highCNI group [38].

In our study, cell immigration was attenuated in the group receiving combined anti-BAFF and low-dose Cyclosporine A treatment which might suggest a beneficial effect of anti-BAFF treatment on intragraft fibrosis.

The highCNI group showed the lowest levels of immune cell infiltration and reduced graft fibrosis, but also displayed slightly increased DKK3 expression on day 28. Which, given the prognostic character of DKK3 in CKD and transplant settings, may be considered unfavorable. As anticipated, the lowCNI group showed the highest levels of cell infiltration and fibrosis as well as a trend toward increased DKK3 expression compared to highCNI and lowCNI+anti-BAFF on day 56, indicating under-immunosuppression. Adding anti-BAFF to lowCNI treatment was associated with reduced B-cell infiltration (CD20 positivity), moderate fibrosis and the lowest DKK3 expression, suggesting the lowest potential for sustained cellular stress and fibrosis.

It is not possible to determine from the available data whether the tentative trends toward changes in DKK3 levels play a causal role in this model and context.

Further analyses with larger sample sizes are required to draw more definitive conclusions regarding the efficacy and safety of anti-BAFF-based immunosuppression following kidney transplantation. Although preclinical studies and early-phase clinical trials have demonstrated that anti-BAFF therapies can effectively reduce B-cell populations and modulate immune responses in transplant models, the current evidence base remains limited, and no anti-BAFF regimen is yet approved for routine use in kidney transplantation. Ongoing and future studies with adequate statistical power are essential to establish the clinical utility and long-term outcomes of this therapeutic approach.

These results suggest that BAFF inhibition may modulate profibrotic processes and may highlight the therapeutic potential of targeting BAFF to prevent chronic allograft dysfunction in the context of under-immunosuppression or non-adherence.

CRediT authorship contribution statement

A. Preiss: Visualization, Validation, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **C. Daniel:** Validation, Investigation, Writing – review & editing. **E. Vonbrunn:** Validation, Investigation, Writing – review & editing. **M. Scharf:** Investigation, Writing – review & editing. **B. Banas:** Visualization, Validation, Conceptualization, Writing – review & editing. **T. Bergler:** Supervision, Methodology, Investigation, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **A. Schuster:** Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization, Writing – review & editing, Writing – original draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.trim.2026.102388.

Data availability

Data will be made available on request.

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