A multicenter registry study of the CD38 antibody daratumumab for the treatment of microvascular inflammation following kidney transplantation

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Abstract

Introduction: Microvascular inflammation (MVI) on kidney biopsy is associated with reduced graft survival following kidney transplantation (KT). CD38-targeting regimens, including the monoclonal antibody daratumumab, have recently emerged as a promising therapeutic strategy to counteract MVI and stabilize graft function.

Methods: Here, we retrospectively collected data on eGFR, albuminuria, kidney allograft pathology, donor specific antibodies (DSA) and donor-derived cell-free DNA (dd-cfDNA) levels from 70 KT patients both prior to and after initiation of daratumumab treatment. Safety signals were also documented.

Results: The study cohort consisted of 59 patients diagnosed with antibody mediated rejection (AMR) and 11 patients showing DSA- and C4d-negative MVI. Median time between transplantation and diagnosis of MVI was 36 months. Daratumumab treatment was initiated at a median of 1.6 months following diagnosis of MVI. A mixed linear model showed stabilization of eGFR from -1.6 ml/min/1.73m^2/month in the year prior to the diagnosis of MVI to +0.3 ml/min/1.73m^2/month after starting daratumumab. Six patients lost their graft during follow-up. Median albuminuria and dd-cfDNA levels decreased early during treatment, whereas the effect on DSA was heterogeneous. Both the number of doses and treatment duration had no measurable impact on outcome.

Conclusions: Our preliminary data suggest efficacy of daratumumab in stabilizing kidney function in KT recipients with MVI.

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KEYWORDS: antibody-mediated rejection; daratumumab; dd-cfDNA; kidney transplantation; microvascular inflammation; outcome

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Microvascular inflammation (MVI)—defined as a combination of glomerulitis and peritubular capillaritis—represents the hallmark histologic lesion of antibody-mediated rejection (AMR) following kidney transplantation (KT) and remains 1 of the leading causes of premature allograft loss.[1] Although AMR early after transplantation has traditionally been treated with plasma exchange and i.v. application of immunoglobulins with good short-term success,[2,3] treatment options for chronic AMR months to years after KT remain limited. Various trials targeting either B cells via rituximab or plasma cells via bortezomib were published with negative results.[4,5] Likewise, inhibiting proinflammatory pathways, such as the complement system or interleukin 6/interleukin 6 receptor, has demonstrated limited efficacy.[6–9]

The current paradigm suggests that donor-specific anti–human leukocyte antigen antibodies (DSAs) produced by plasma cells bind to graft endothelium and cause damage either via complement-dependent cytotoxicity or cell-mediated cytotoxicity (antibody-dependent cellular cytotoxicity), the

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Lay Summary

In kidney transplant patients, microvascular inflammation is the hallmark histologic lesion of antibody-mediated graft rejection and a leading cause of premature allograft loss. Until today, treatment options have been limited. Preliminary evidence suggested efficacy of targeting CD38, a transmembrane protein highly expressed on natural killer (NK) cells and plasma cells, in reversing microvascular inflammation. Here, we present data from a multicenter retrospective cohort study on the use of daratumumab (anti-CD38) in 70 kidney transplant patients with microvascular inflammation. A decline in allograft function (estimated glomerular filtration rate) in the 12 months before treatment initiation was successfully reversed by daratumumab. Injury markers, such as albuminuria and cell-free donor-derived DNA levels, declined early, accompanied by reversal of microvascular inflammation in 50% of patients on follow-up graft biopsy. The safety profile was generally favorable. These data support the efficacy of daratumumab in stabilizing graft function in kidney transplant patients with microvascular inflammation.

latter primarily being mediated by NK cells or monocytes.[10] However, MVI in the absence of detectable DSA or positive C4d staining is common and has been recognized as a new phenotype in the Banff classification in 2022.[11] The underlying mechanism of this phenotype is still not fully understood, but missing self-recognition by alloreactive NK cells has been proposed as a potential contributing mechanism.[12] Both entities, AMR and MVI (DSA/C4d negative), significantly increase the risk of graft failure compared with patients without MVI on allograft biopsy.[13,14]

Recently, targeting CD38, a multifunctional glycoprotein highly expressed on both plasma cells and NK cells, has become a promising strategy in the treatment of AMR. The CD38 antibody daratumumab, currently approved for the treatment of multiple myeloma, has demonstrated effectiveness in reversing AMR clinically, but also on a molecular level, in several case reports and smaller case series.[15–19] Another antibody targeting CD38, felzartamab, has recently shown promising results in a phase 2 study,[20,21] and a phase 3 study is currently ongoing.[22]

Despite much enthusiasm, many questions remain with respect to the optimal dose and treatment duration as well as the long-term effect of anti–CD38-containing regimens on allograft function and recipients' susceptibility to infectious complications. Moreover, it is currently unclear whether CD38 antibodies are also effective in DSA-negative MVI. To address these questions, we retrospectively collected clinical data on patients treated with daratumumab for MVI following KT at 8 transplant centers in Germany and Austria.

METHODS

Patients

In this retrospective, multicenter study, data from adult KT patients treated with daratumumab for biopsy-confirmed AMR or DSA-negative C4d-negative MVI according to the Banff 2022 classification[11] at 7 German transplant units (Berlin, Hamburg, Hannover, Leipzig, Muenster, Ludwig-Maximilians University Munich, and Regensburg) and 1 Austrian unit (Vienna) were entered into the daratumumab registry study database. From 89 patients recorded in the database on March 31, 2026, we included 70 patients with at least 3 months of clinical follow-up and an index biopsy with an unequivocal histopathologic diagnosis of AMR or DSA-negative C4d-negative MVI in this analysis (Supplementary Figure S1). Daratumumab was given off label in the absence of validated therapeutic alternatives after individual cost coverage by the health insurance providers was obtained. Patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethic committees of the participating centers.

Clinical data

Participating centers reported available data on renal function (estimated glomerular filtration rate [eGFR] using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation) and urinary albumin-to-creatinine ratio (in mg/g) at the following time points: at the index biopsy (first diagnosis of MVI), at the first dose of daratumumab (baseline), and at 3, 6, and 12 months thereafter. To compare the eGFR trajectory before and after daratumumab treatment, data on eGFR 3, 6, and 12 months before the index biopsy were also collected. Data on therapeutic interventions targeting MVI before initiation of daratumumab were also recorded. Graft failure was defined as permanent reinstitution of hemodialysis. Infusion-related reactions and infectious complications during treatment were reported and specified by the treating physicians. A serious adverse event was defined as a complication requiring hospitalization.

Blood for donor-derived cell-free DNA (dd-cfDNA) levels was collected in certified blood collection tubes (Streck Corp) during clinical routine at varying intervals defined by the participating centers. Following shipment to the processing laboratory, dd-cfDNA levels were determined using the droplet digital polymerase chain reaction method, as previously described, and reported as copies/ml and percentage of total cfDNA.[23,24] dd-cfDNA levels at baseline (before the first dose of daratumumab), after 2 to 12 weeks (first available follow-up), and at months 6 and 12 were included in the analysis.

Screening and specification of DSA was done according to center practice in the local tissue typing laboratories following the standards of the European Federation of Immunogenetics using Luminex-based LABScreen single-

antigen bead assays (One Lambda Thermo Fisher Scientific). DSAs were considered positive above a mean fluorescence intensity (MFI) threshold of 1000 (Berlin, Hannover, Regensburg, and Vienna) and 1500 (Hamburg, Leipzig, Muenster, and Munich). In Vienna, MFI values are reported in categories (category 1: MFI 1000–2000; 2: 2001–5000; 3: 5001–10,000; 4: >10,001). Therefore, the highest value within the respective category was used for analysis.

All biopsy specimens were primarily assessed by the local nephropathologists using established protocols and were classified according to the latest Banff classification at the time of biopsy sampling. C4d staining was performed using immunohistochemistry on paraffin-embedded, formalin-fixed tissue sections. Because the Banff 2022 classification introduced 2 new entities of interest (MVI, DSA-/C4d negative, and probable AMR), all biopsy specimens were reclassified according to Banff 2022 based on the reported lesion scores and DSA findings. Mixed rejection (AMR/T-cell–mediated rejection) was defined as having MVI including glomerulitis with simultaneous presence of T-cell–mediated rejection ≥ IA lesions.

Daratumumab treatment schedules

As there is no established standard protocol for treatment with daratumumab in the context of MVI following KT, patients were treated according to local practice. Thus, the intervals and routes of daratumumab administration (i.v. vs. s.c.) differed between the centers. To investigate whether there is a difference in efficacy between more intense and less intense protocols, patients with at least 6 months of follow-up were categorized into 3 groups, depending on which regimen was applied. Patients assigned to group 1 received intensive daratumumab therapy with at least 10 doses within 6 months based on the standard myeloma protocol: 16 mg/kg body weight i.v. or a fixed dose of 1800 mg s.c. weekly for 8 weeks, followed by 8 doses every 2 weeks and monthly doses thereafter. Patients with minor protocol deviations (occasionally missed or postponed doses) were also assigned to group 1. Patients with a less intensive protocol with longer application intervals (e.g., monthly) were assigned to group 2. Patients categorized into group 3 had early withdrawal of therapy (<8 weeks) because of adverse events or graft failure.

Statistical analysis

Statistical analyses were performed with IBM SPSS Version 29 and R version 4.5.1.[25] Descriptive statistics are reported using median with interquartile range (IQR) for continuous variables and absolute numbers (percentage of total) for nominal variables. The Mann-Whitney *U* test was used for testing continuous variables between independent samples. For testing continuous variables between dependent samples, a nonparametric paired *t* test was computed, using function npar.t.test.paired() from R package nparcomp.[26] A linear mixed model for eGFR was estimated with time, daratumumab, and interaction between time and daratumumab as fixed effects. Time at index biopsy was defined as 0 with up to 3 measures before (–12, –6, and –3 months). Time between index biopsy and first daratumumab differed between patients (Supplementary Figure S2) but was set to the median (=1) for all patients, as the main interest was to compare eGFR before and after initiation of daratumumab, and it was assumed that the time between index biopsy and start of daratumumab has no relevant effect. After initiation of daratumumab, the model included up to 3 measures (3, 6, and 12 months). The patient identifier was used as the random intercept. Marginal and conditional R^2 values are reported as measures for explained variance. As sensitivity analysis, we conducted a mixed model including a nonlinear term for time (time^2) and the time between index biopsy and first daratumumab as additional fixed effects. All tests performed were 2 sided. All analyses are explorative without adjustment for multiple testing and do not allow for confirmatory conclusions. In general, pairwise deletion was performed if single values were missing. An eGFR of 5 ml/min per 1.73 m^2 was imputed for patients who experienced graft loss during follow-up. Figures were generated using Prism Software Version 10.6.1 and R.

RESULTS

Baseline characteristics

We report the results of 70 KT patients who received daratumumab for the treatment of biopsy-proven MVI. Most biopsies (67 of 70) were triggered by graft dysfunction. In most patients (81%), MVI occurred >6 months after KT. Median time between KT and the index biopsy was 36 months (IQR, 9–110 months). At the time of the index biopsy, 46 (66%) patients had detectable DSA, of which 31 (44%) were classified as *de novo* DSA. Median eGFR at the time of the index biopsy was 31 ml/min (IQR, 18–42 ml/min) and albuminuria was 454 mg/g creatinine (IQR, 122–1080 mg/g) (Table 1).

On the basis of the Banff 2022 classification, 14 patients (20%) had active AMR on index biopsy, with 11 of 14 biopsies being C4d positive. Forty patients had additional chronic glomerulopathy lesions, classifying as C4d-positive chronic active AMR in 22 patients and C4d-negative chronic active AMR in 18 patients. Five additional patients (7%) were diagnosed as having mixed (AMR/T-cell–mediated rejection) rejection. Eleven patients (16%) fulfilled the criteria of DSA-negative, C4d-negative MVI. Median MVI score (glomerulitis + peritubular capillaritis) was 4 (IQR, 3–5), with 96% of index biopsies having an MVI sum score ≥2 (Supplementary Table S1). The individual diagnostic features and Banff category 2 phenotypes are summarized in Supplementary Table S2.

Characteristics of daratumumab therapy

Daratumumab treatment was initiated at a median of 1.6 months following the diagnosis of MVI (Table 1). At that time, 41 patients (59%) had already received alternative treatment regimens for AMR (Supplementary Table S3). Five patients required hemodialysis at the time of daratumumab initiation.

Table 1 | Patient characteristics (n = 70)

Characteristic	Value
At transplantation	
Age, yr	45 (32–55)
Female sex	31 (44)
Previous kidney transplantation	23 (33)
vPRA positive	28 (40)
vPRA, %	80 (47–96)
Preformed DSA	18 (26)
Donor age, yr	54 (42–61)
Living donation	26 (37)
ABO incompatible	8 (11)
Cold ischemia time, min[a]	659 (158–985)
At diagnosis of AMR/MVI	
Time between transplantation and index biopsy, mo	36 (9–110)
Late AMR/MVI (>180 d after KT)	57 (81)
DSA positive	46 (66)
De novo DSA	31 (44)
Maintenance immunosuppression	
Tacrolimus/mycophenolate/prednisolone	55 (79)
Other	15 (21)
eGFR (CKD-EPI) at index biopsy, ml/min per 1.73 m^2	31 (18–42)
Albuminuria at index biopsy, mg/g creatinine	454 (122–1080)
Other treatment before daratumumab[b]	41 (59)
Time between AMR/MVI diagnosis and first dose of daratumumab, mo	1.6 (0.6–4.5)

AMR, antibody-mediated rejection; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DSA, donor-specific anti–human leukocyte antigen antibody; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; MVI, microvascular inflammation; vPRA, virtual panel reactivity.
[a]Patients after living donation excluded.
[b]For specific regimens, see Supplementary Table S3.
Data are presented as median (interquartile range) or number (percentage of total).

Table 2 | Treatment status 6 months after initiation of daratumumab therapy

Variable	Value
Patients still receiving therapy	26 (44)
Under surveillance after treatment	30 (51)
Median duration of therapy, mo	4.8 (2.7–5.3)
Therapy discontinued because of adverse events or ESRD	3 (5)
Median duration of therapy, mo	1.6 (0.7–1.8)
Treatment protocol	
Group 1	19 (32)
Group 2	37 (63)
Group 3	3 (5)
Median cumulative No. of doses after 6 mo of treatment	
Group 1	15 (12–16)
Group 2	7 (6–9)
Group 3	3 (3–8)
Overall cohort	8 (6–12)

ESRD, end-stage renal disease.
Data are shown as number (percentage of total) or median (interquartile range).

Treatment regimens varied considerably between patients and transplant centers. At 6 months, 26 of 59 patients (44%) were still on daratumumab therapy, whereas 30 patients (51%) were under surveillance after a median treatment duration of 4.8 months (IQR, 2.7–5.3 months). Nineteen patients (32%) had received an intensified regimen analogous to the scheme established for the treatment of multiple myeloma, with a median of 15 (IQR, 12–16) daratumumab doses within 6 months (group 1). Thirty-seven patients (63%) in the less-intense treatment group (group 2) had received a median of 7 (IQR, 6–9) doses by 6 months. Three patients (5%) had early withdrawal of therapy (group 3). Two withdrew because of nonreversible dialysis-dependent graft failure. The other patient had recurrent infectious complications (Table 2).

All patients had at least 3 months of follow-up after initiation of daratumumab treatment. The 6- and 12-month follow-up data were available for 59 (84%) and 38 (54%) of patients, respectively.

Adverse events

Infusion-related reactions were observed in 36 (51%) patients, most frequently during the first application of daratumumab. The most common symptoms were nausea, dyspnea, chest pain, and unspecific reactions, like myalgia, headache, or shivering. Two patients required inpatient monitoring because of severe dyspnea and a hypersensitivity reaction. In both patients, daratumumab was continued and well tolerated after the first dose (Supplementary Table S4).

Infections occurred in 33 (47%) patients. Treatment intensity (group 1 vs. group 2) had no measurable impact on the incidence of infectious complications (Supplementary Table S4). The most common infections were urinary tract infections, followed by respiratory tract infections and gastroenteritis. Eleven patients had cytomegalovirus viremia, and organ involvement manifesting as cytomegalovirus colitis was documented in 3 patients. Three patients had biopsy-proven polyomavirus-associated nephropathy, which had already been present in all patients before daratumumab therapy. One patient developed a primary Epstein-Barr virus infection. Fifteen infectious complications were graded as severe and required hospitalization. Therapy was discontinued in 4 patients because of infections. No patient died during the observation period (Supplementary Table S4).

Clinical outcome

In the 12 months before the diagnosis of MVI, median eGFR declined from 47 (IQR, 37–63) ml/min per 1.73 m^2 to 31 (IQR, 18–42) ml/min per 1.73 m^2. Treatment with daratumumab resulted in stabilization of median eGFR over 12 months (Supplementary Table S5 and Supplementary Figure S3A). Individual eGFR decreased by 13 ml/min per 1.73 m^2 in the 12 months before the diagnosis of MVI but increased by 5 ml/min per 1.73 m^2 in the 12 months after treatment initiation (Supplementary Table S5 and Figure 1a). Sensitivity analysis confirmed the increase in eGFR after

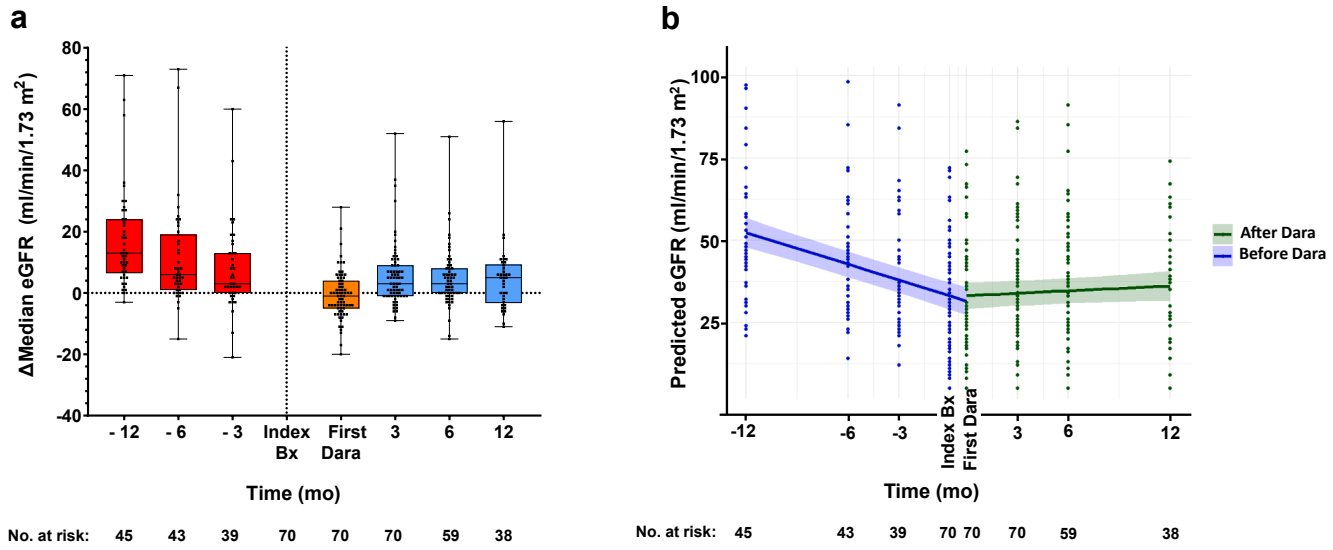


Figure 1 | Estimated glomerular filtration rate (eGFR) trajectories before versus after initiation of daratumumab treatment. (**a**) Median individual changes in eGFR over 12 months prior to treatment initiation relative to the eGFR at the time of the index biopsy (Index Bx) (red bars) are illustrated, along with changes in eGFR relative to the time of daratumumab treatment initiation (first Dara) (orange bar) and over the next 12 months (blue bars). (**b**) eGFR trajectories before (blue) and after (green) treatment initiation are depicted, as predicted by the linear mixed regression model including original data points.

treatment initiation in the subgroup of 38 patients with at least 12 months of follow-up (Supplementary Figure S3B). Of 4 patients, 3 could be taken off dialysis early after initiation of daratumumab. Four patients who were free from dialysis at treatment initiation experienced graft loss within 12 months of the index biopsy. These patients had an eGFR lower than 15 ml/min per 1.73 m^2 before initiation of daratumumab. One patient remained on dialysis despite daratumumab treatment and had early termination of therapy. A linear mixed model of the eGFR trajectories revealed a mean monthly decline of –1.6 ml/min per 1.73 m^2 in the 12 months before initiation of daratumumab, whereas there was a mean monthly increase of 0.3 ml/min per 1.73 m^2 in the 12 months after starting treatment (Supplementary Table S6 and Figure 1b). Sensitivity analysis using a mixed model including a nonlinear term for time (time^2) and the time between index biopsy and first daratumumab as additional fixed effects revealed comparable results (Supplementary Table S7 and Supplementary Figure S4).

Albuminuria decreased by 83% from 454 (IQR, 88–1095) mg/g creatinine at treatment initiation to 76 (IQR, 25–247) mg/g creatinine after 12 months of daratumumab treatment ($P < 0.001$; Figure 2a and Supplementary Table S5). This finding was also confirmed in the subgroup of 32 patients with at least 12 months of follow-up (Supplementary Figure S5).

Blood biomarkers

We observed a decline of dd-cfDNA levels (from 1.6% of total cfDNA [IQR, 0.7%–3.7%] to 0.3% [IQR, 0.2%–0.8%]; $P < 0.001$) within 12 weeks after treatment initiation (Figure 2b and Supplementary Table S5). Median dd-cfDNA values remained low at months 6 and 12. One patient with a marked increase of dd-cfDNA at follow-up experienced graft loss within 3 months.

Of the 46 patients with available DSA data after 6 months of therapy, 22 (48%) were DSA positive. At this time, 3 patients who were DSA negative at the time of the index biopsy had developed *de novo* DSA. Eleven patients with DSA-positive MVI on index biopsy had no more detectable DSA. In the 19 patients with persistent DSA, daratumumab had no impact on MFI values (Figure 2c and Supplementary Table S5).

Biopsy results

Follow-up biopsies were obtained from 52 patients (74%) after a median of 3.7 (IQR, 2.6–6.1) months of daratumumab therapy (Supplementary Table S8). The clinical treatment response at 3 months was comparable in patients with and without follow-up biopsy (Supplementary Table S9). Histologically, resolution of MVI was observed in 27 patients (52%). Ten of these patients showed residual chronic AMR with isolated chronic glomerulopathy lesions. Median MVI score decreased from of 4 (IQR, 3–5) on index biopsies to 1 (IQR, 0–3) on follow-up biopsies ($P < 0.001$; Supplementary Table S8, Figure 3a, and Supplementary Figure S6). Accordingly, the activity score, recently suggested by Vaulet *et al.*[27] and mentioned in the most recent Banff 2024 meeting report,[28] decreased significantly ($P < 0.001$) from a median of 6 (IQR, 4–7) on index biopsies to 3 (IQR, 1–4) on follow-up (Supplementary Figure S7A).

Transplant glomerulopathy (chronic glomerulopathy lesions) was present in 50% (26 of 52) of patients on follow-up biopsy. Evolution of the chronicity score[27,28] was highly

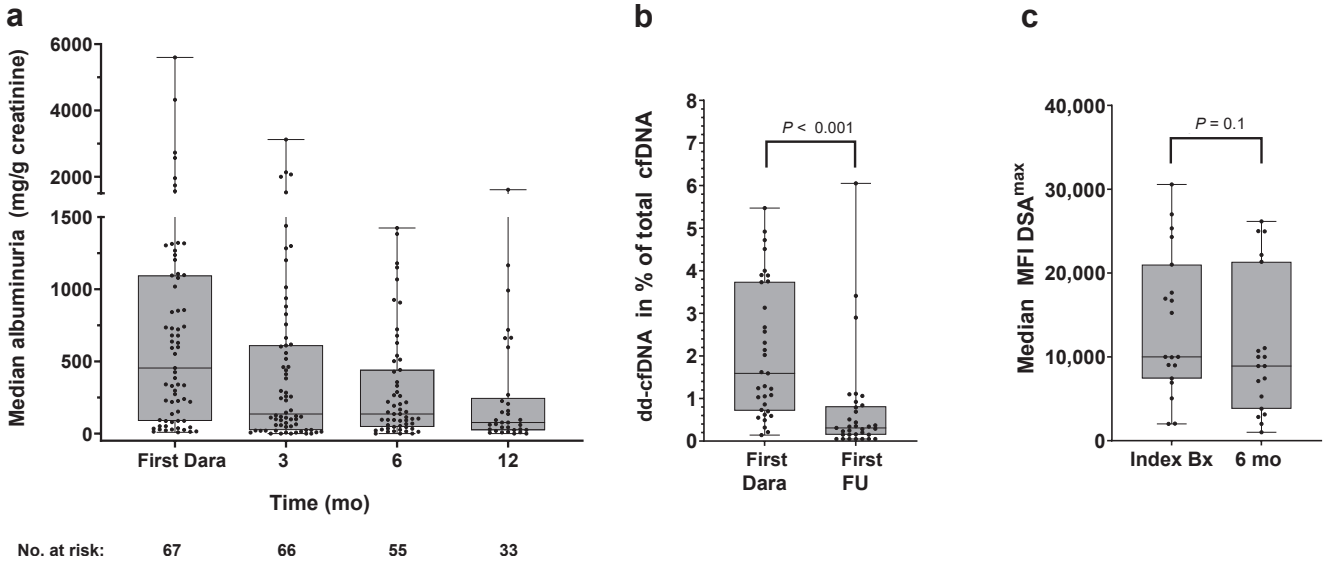


Figure 2 | Biomarkers before and after treatment initiation. (**a**) Albuminuria levels (mg/g creatinine) at daratumumab treatment initiation (first Dara) and over the next 12 months. $P < 0.001$ for all time points relative to albuminuria at treatment initiation. (**b**) Donor-derived cell-free DNA (dd-cfDNA) levels (in percentage of total cfDNA) before treatment initiation (first Dara) and at first follow-up (FU). N = 33. (**c**) Mean fluorescence intensity (MFI) values of persistent donor-specific anti–human leukocyte antigen antibodies (DSAs) at the time of the index biopsy (Index Bx) and 6 months after initiation of daratumumab treatment (6 mo). In case of multiple persistent DSAs, the MFI of the DSA with the highest MFI (MFI DSA^{max}) is shown. N = 19.

variable between patients and decreased from a median of 6 (IQR, 3–9) at baseline to 4.5 (IQR, 3–9) on follow-up biopsy ($P = 0.82$; Supplementary Figure S7B). The individual changes in Banff phenotypes following daratumumab treatment are visualized in Figure 3b.

Subgroup analysis of patients with DSA-negative C4d-negative MVI

In the subgroup of 11 patients with DSA-negative C4d-negative MVI on index biopsy, the effect of daratumumab treatment on eGFR and albuminuria levels

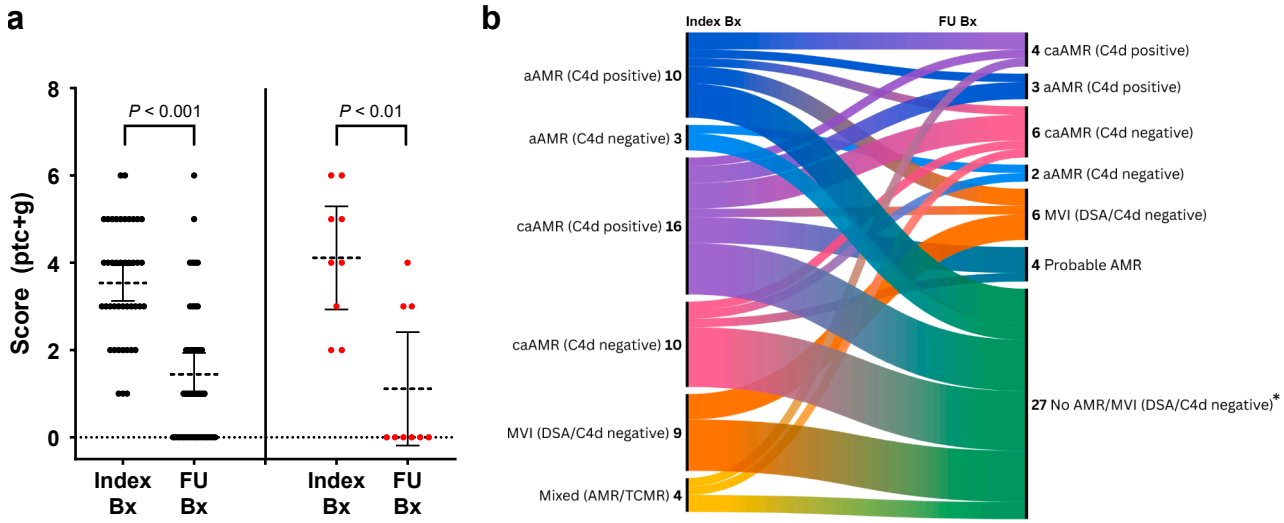


Figure 3 | Evolution of biopsy findings following daratumumab treatment. (**a**) Changes in median microvascular inflammation (MVI) sum score are illustrated between the index biopsies (Index Bx) and the first follow-up biopsies after initiation of daratumumab (FU Bx). The subgroup of DSA-negative, C4d-negative MVI is depicted on the right (n = 9), and all other Banff 2022 category 2 phenotypes are shown on the left (n = 43). (**b**) Sankey plots of the dynamics of MVI under daratumumab treatment are shown, illustrating individual changes in Banff categories between index and follow-up biopsies. *Including 10 patients with isolated chronic glomerulopathy lesions. Numbers indicate individual group sizes. Total n = 52. aAMR, active antibody-mediated rejection; AMR, antibody-mediated rejection; caAMR, chronic active antibody-mediated rejection; DSA, donor-specific anti–human leukocyte antigen antibody; g, glomerulitis; ptc, peritubular capillaritis; TCMR, T-cell–mediated rejection.

was comparable to all other patients (Supplementary Figure S8 and Supplementary Table S10). Likewise, intragraft inflammation decreased, demonstrated by lower MVI sum scores as well as lower activity scores following daratumumab treatment (Figure 3a and Supplementary Figures S6–S8). As with the overall cohort, evolution of chronicity scores was highly variable between patients (Supplementary Figure S7B). Of 9 follow-up biopsies, 6 showed complete resolution of MVI (Figure 3b).

Further subgroup analyses

Daratumumab treatment was more effective at 6 months in terms of eGFR stabilization in early compared with late MVI and in active compared with chronic active AMR at the time of the index biopsy. The effect on albuminuria, however, was not different. Efficacy of daratumumab was comparable between the more and the less intense treatment group (Supplementary Figure S9). Likewise, treatment duration (<6 vs. ≥6 months) had no impact on either eGFR slope or albuminuria between months 6 and 12. Daratumumab proved equally effective regardless of the presence or absence of mixed rejection or whether patients received prior treatment for MVI or not. Improvement in eGFR and reduction of albuminuria was independent of MVI resolution on follow-up biopsy (Supplementary Table S10).

DISCUSSION

In this retrospective, multicenter study involving 70 KT patients with biopsy-confirmed MVI, treatment with daratumumab resulted in stabilization of graft function and histologic resolution of MVI, with 52% of patients showing no activity on follow-up biopsies. Our findings are in line with several case reports and case series, which also suggested improvement of graft function and reduction of MVI through the use of daratumumab.[15,16,29,30] However, this study is the first to show stabilization of eGFR slope in that daratumumab treatment resulted in a reversal of individual eGFR decline from –13 ml/min per 1.73 m^2 in the year before the diagnosis of MVI to an increase of 5 ml/min per 1.73 m^2 at 12 months following treatment initiation. Contrary to previous reports,[20,30] patients in our cohort had worse graft function at the start of daratumumab therapy, highlighting the real-world characteristics of our study cohort and suggesting a treatment effect even in late chronic active AMR. Four patients lost their graft despite treatment, indicating limited efficacy in patients with advanced graft failure.

In our cohort, stabilization of eGFR was accompanied by rapid reduction of dd-cfDNA levels, highlighting the clinical value of this biomarker as an injury marker in the context of MVI.[23,31,32] We also noted rapid decline in albuminuria, which has not been consistently reported to occur with anti-CD38 therapies,[20,30] suggesting that albuminuria can also serve as an easily accessible clinical injury marker in MVI.

Previous studies have documented a modest effect of CD38-targeting regimens on anti–human leukocyte antigen antibody levels in both patients with AMR[20,30] and highly sensitized patients in the context of desensitization treatment.[33,34] In our cohort, a relevant proportion of patients with DSA at the time of the index biopsy had no available follow-up DSA data (13 of 59). However, in 19 of 46 patients with available data, DSA persisted with comparable MFI values, and 3 more patients developed *de novo* DSA during treatment. These data support the hypothesis that the treatment effect of daratumumab is not primarily mediated by depletion of antibody-producing plasma cells but by elimination of effector cells, such as CD38-positive NK cells.[12] This hypothesis is supported by both conventional histology data as well as suppression of NK cell-based molecular transcripts in biopsies from patients treated with anti-CD38 antibodies for MVI.[21,35] Importantly, this is the first report to include patients fulfilling the recently implemented Banff criteria of DSA-negative C4d-negative MVI.[11] Subgroup analysis revealed a comparable clinical efficacy in these patients, further supporting the involvement of DSA-independent mechanisms in the pathophysiology of MVI.[36]

Clinical stabilization of graft function was accompanied by amelioration of MVI on follow-up biopsy. Median MVI score (glomerulitis + peritubular capillaritis) was reduced by 75% (4 to 1) with 52% of all patients having no more MVI activity on their first control biopsy, which was taken at a median of 3.7 months after initiation of treatment, when most patients were still receiving daratumumab. This is comparable to the response rate of 56% recently reported in a cohort of 16 living KT patients treated with daratumumab for 10 months[30] and a rate of 64% with an MVI sum score of 0 in the recent felzartamab trial after 24 weeks of therapy.[20] In both studies, recurrence of AMR occurred in 10% to 50% of patients after stopping daratumumab, preceded by an increase in dd-cfDNA in most patients. In our cohort, no systematic follow-up biopsies were performed after daratumumab was stopped, and longitudinal dd-cfDNA testing was not systematically performed in all participating centers. Long-term follow-up of our cohort should allow us to assess recurrence rate, the response to retreatment, and the value of repeat dd-cfDNA testing in guiding treatment decisions and assessing outcome.[37,38]

Despite transient depletion of both NK cells and plasma cells in addition to administration of conventional immunosuppression, daratumumab treatment was generally well tolerated, and the safety profile was comparable to what has been reported for patients treated for multiple myeloma.[39] Nonetheless, we documented infectious complications in 47% of patients, with 4 patients discontinuing treatment because of recurrent infections, more than what has been published in the recent felzartamab trial.[20] It can be speculated whether these differences are related to differences in the mechanism of action of daratumumab compared with felzartamab.[40] As infectious complications are frequent in this patient population, the lack of a control group in our

study does not allow for firm conclusions. Given that long-term administration of daratumumab profoundly impairs both NK and B-cell immunity,[41,42] caution is warranted and long-term follow-up will be critical.

In the absence of an established treatment protocol, administration of daratumumab varied considerably in terms of both frequency and treatment duration in our cohort. Interestingly, we found no difference between an intense (≥10 doses) and a less intense treatment regimen (<10 doses at month 6) with regard to eGFR slope and reduction of albuminuria. Moreover, a short treatment course (<6 months) proved equally effective at 12 months compared with a prolonged therapy (≥6 months). These findings are important as they should allow for cost savings and preservation of resources. They also support the proposal of a recently published consensus-based treatment standard to administer daratumumab weekly over 4 weeks, followed by monthly doses for 3 to 6 months.[43] Subgroup analysis further suggested efficacy in the treatment of early (<6 months after KT) AMR. Given the limited long-term efficacy of conventional immunosuppressive regimens for early AMR, daratumumab might also become a valuable treatment option in this clinical scenario. Last, daratumumab treatment was also effective in patients with mixed rejection, as these patients are commonly excluded from clinical trials.

We observed clinical stabilization of graft function independent of residual MVI on control biopsies. This finding is intriguing as it challenges the central role for conventional histology in determining treatment responses. Support for this disconnect is provided by the rapid decline in dd-cfDNA, a marker of active cell death, even in patients with persistent histologic inflammation. This implies an "injury arrest," where cytotoxicity is abrogated before the infiltrate is fully cleared. Alternative hypotheses remain speculative (e.g., whether the residual cellular infiltrate after daratumumab treatment differs from the cells underlying MVI before treatment, whether control biopsies in our cohort were performed too early to document complete resolution of inflammation following the start of daratumumab treatment, or whether the effect of daratumumab occurs outside the allograft in some patients). The latter hypothesis is refuted by a recently reported reduction of NK-related transcripts in biopsies following felzartamab treatment.[21]

Our study has limitations. First, histopathology was read and categorized by the local nephropathologists and not by a central adjudication committee, which is why we cannot rule out a center-specific bias in histopathology reading and scoring. Second, given the retrospective design of our study and the lack of a control group, we acknowledge that all the findings reported here have to be interpreted cautiously. It is likely that both eGFR slope before and the extent of MVI on the index biopsy have influenced treatment decisions, duration, and dosing. Moreover, the relatively small number of patients in each of the different histopathologic subgroups precludes any final conclusions on which of these phenotypic subtypes eventually will benefit most from anti-CD38 treatment strategies, and which potentially less. Moreover, follow-up for the current analyses was relatively short; and many questions, most notably the effect of daratumumab on long-term allograft function and the long-term susceptibility to infection and cancer development in these patients, still need to be answered.

Nevertheless, the histologic resolution of MVI in 50% of patients as well as the stabilization of eGFR following daratumumab treatment in a broad spectrum of patients with AMR/MVI in our multicenter cohort support the recent enthusiasm for CD38-targeting regimens in KT.

DISCLOSURE

MO is a consultant of Insight Molecular Diagnostics Inc (Nashville, TN). JB, KB-K, and ES are employees of Chronix Biomedical GmbH (an Insight Molecular Diagnostics Inc. company). AA has received travel grants from iMDx. FH has received grant support and honoraria from MSD, Hansa Biopharma, and Chiesi. GAB has received grant support from Biogen; and consulting fees from Argenx, Biogen, Takeda, and Alexion. KB has received grant support from Alexion, Astellas, AstraZeneca, Chiesi, CSL Behring, Otsuka, Stada, Takeda, iMDx, Biogen, and HiBio; consulting fees from Aicuris, Alexion, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Carealytics, CareDx, Chiesi, CSL Behring, Fresenius, Hansa, HiBio, MSD, Natera, Neovii, Paladin, Pfizer, Pirche, Sanofi, Stada, Takeda, Veloxis, Vifor, and Xenothera; and honoraria from Astellas, AstraZeneca, iMDx, Chiesi, Fresenius, Hansa, MSD, Neovii, Paladin, Sanofi, and Takeda. He also received travel support from iMDx, AstraZeneca, Chiesi, Hansa, HiBio, MSD, Neovii, Paladin, Stada, Takeda, and Veloxis. All the other authors declared no competing interests.

DATA STATEMENT

Sharing individual participant data with third parties was not specifically included in the informed consent form for the study, and unrestricted sharing of these data may pose the threat of revealing participant's identities, as permanent data anonymization was not performed. However, the data may be shared on reasonable request for academic research collaborations that fulfill General Data Protection Regulation standards after submission of a methodologically sound proposal to daniel.zecher@ukr.de. To gain access, data requesters will need to sign a data access agreement and obtain approval by the local institutional review board.

AUTHOR CONTRIBUTIONS

TD analyzed data and wrote the manuscript. KAM, GAB, AA, FH, KB, DR, CH, MK, FG, JK, SB, SR, SK, TS, and BB contributed conceptually, provided patient data, and contributed to the writing of the manuscript. MP performed statistical analyses. JB, KB-K, ES, and MO analyzed patient samples. DZ designed the study, analyzed data, and wrote the manuscript.

Supplementary material is available online at www.kidney-international.org.

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