Tubulointerstitial fibrosis is the terminal consequence of chronic active inflammation of any cause. The pathophysiology is driven by an imbalance between tubular repair mechanisms counteracting injury and endothelial-mesenchymal transition of these cells and resident fibroblasts as well as infiltration of myofibroblasts from the circulation leading to extensive deposition of extracellular matrix (1). TGF-β signaling through the intracellular Smads superfamily is the most prominent mediator of renal fibrosis (2).

In the setting of renal transplantation, the trigger of chronic inflammation is the continuous ongoing cellular and humoral alloimmune response to the graft, which per se leads to inflammation of the tubulointerstitial compartment as well as a progressive narrowing of the graft vasculature. This hypothesis is supported by recent findings in transcriptomics analyses of biopsies, which suggest that graft deterioration is more dependent on continuing nephron injury through humoral alloimmunity than fibrogenesis (3,4). This view is further reinforced by biopsy findings of patients who have attained a state of immunologic allograft tolerance, where even long after transplantation, no inflammation, tubulointerstitial fibrosis, and arteriolar hyalinosis can be detected (5,6).

Hypoperfusion and consequent hypoxia of the grafts of patients on maintenance immunosuppression have also been shown to trigger endothelial-mesenchymal transition of tubule cells, specifically in regions with physiologically low oxygen tension, such as the renal medulla (7). On top of these alloimmune-mediated processes, calcineurin inhibitor toxicity and preexisting arterial hypertension, which may be aggravated by the immunosuppressive regimen, are the main drivers of fibrosis. These processes and quantification of humoral immunity and fibrosis have been described and rated in the Banff renal allograft pathology consensus reports and original papers (8).

The time course and evolution of the initiation and progression of interstitial fibrosis and its relation to deteriorating excretory graft function have nicely been shown by Nankivell et al. (9). In a recent update of an extended follow-up, the same investigators showed that tacrolimus as the current standard calcineurin inhibitor therapy prevents the development of early inflammation and fibrosis as well as acute arteriolaropathy better than cyclosporin. After the first year, however, the rate of progression of these pathologic features remains the same in cyclosporin- and tacrolimus-treated patients (10), which also fits the findings of Stegall et al. (11), who did not find differences in the progression of Banff chronic changes in the interstitium (ci) scores between years 1 and 5 in tacrolimus- compared with sirolimus-treated patients.

So far, it remains speculative whether treatment of early inflammation will, in fact, lead to less fibrosis and less development of de novo donor-specific anti–HLA antibodies (dnDSAs) and chronic antibody–mediated rejection. Rush et al. (12) found in their earlier studies that treatment of initial subclinical cell–mediated rejection with steroids might be beneficial for the preservation of eGFR as a proxy for fibrosis and long-term outcomes. However, a subsequent study with a more contemporary immunosuppressive regimen found only a 5% rate of subclinical cellular rejection in protocol biopsies obtained within the first 6 months (13). García-Carro et al. (14) analyzed sequential surveillance biopsies obtained at 6 weeks and 1 year after engraftment to test the hypothesis of whether histologic categories at week 6 could predict the development of interstitial fibrosis and dnDSAs at 1 year. The main finding was that early inflammation was associated with dnDSAs at 1 year, regardless of the presence of interstitial fibrosis in the 6-week biopsy. Inflammation and subclinical antibody–mediated rejection in 1 year have been shown recently to be independent predictors of fibrosis and subsequent graft loss (15).

Existing fibrosis in very early allograft biopsies is usually derived from the deceased donor and does not constitute a main risk factor for delayed graft function (DGF), which is more a consequence of acute tubular damage. A recent Banff consensus paper addressed the issue of histopathologic scoring of preimplantation biopsies (16). Gelines et al. (17) found in their single-center analysis that fibrosis in preimplantation biopsies did not increase the risk of DGF but was predictive of the subsequent extent of fibrosis and tubular atrophy at 12 months. However, inflammation of the donor organ in preimplantation biopsies was independently associated with the risk of DGF, but causality could not be established (18). It is an appealing possibility that grafts experiencing DGF as a consequence of systemic inflammation and hypoperfusion in the donor and ischemia-reperfusion injury should have an elevated risk of developing progressive tubulointerstitial...
fibrosis and premature graft loss. In fact, many but not all studies reported a strong independent association of DGF and graft survival (19).

In this issue of the Clinical Journal of the American Society of Nephrology, Heilman et al. (20) specifically addressed this burning topic of whether the progression of interstitial fibrosis determined by the Banff ci score was modified by DGF. The investigators made use of sequential management biopsies obtained within the first year after transplantation between 2003 and 2014. The main outcome was the evolution of changes in the Banff ci score between the DGF and primary graft function. DGF was defined as dialysis dependency in the first week after transplantation. Paired biopsies were available for 155 patients with DGF and 283 patients without DGF. The main unexpected finding was that a Banff ci score >0 in postreperfusion biopsies was independently associated with higher odds of DGF but that the progression of fibrosis in the first year was not different between the DGF and non-DGF group. Even when the DGF group was dichotomized into longer (≥9 days) versus shorter (7>DGF<9 days) dialysis dependency, there was no difference in the slope of fibrosis progression in the multivariable mixed linear regression models.

Furthermore, the investigators did not find an association of DGF with graft survival in the cohort transplanted after 2011, which fits with their histologic findings at 1 year. It is notable that DGF transplants performed before 2012 exhibited such an association compared with primary functioning grafts. However, as discussed above, most of the larger registry analyses showed a strong independent association of DGF with graft attrition. What could explain this difference?

First, donor characteristics differed between the DGF and primary function groups. The DGF group consisted of more men donors after circulatory death with lower terminal eGFR and longer cold ischemic time. Second, the authors observed an era effect; lower graft survival rates at 3 years were only observed in patients with DGF who had been engrafted before 2012 but not thereafter. This may be attributed to procedural changes described, such as different induction therapy. Until 2011, rabbit antithymocyte globulin was used and thereafter, alemtuzumab, and patients without DGF. The main unexpected finding was that a Banff ci score >0 in postreperfusion biopsies was independently associated with higher odds of DGF but that the progression of fibrosis in the first year was not different between the DGF and non-DGF group. Even when the DGF group was dichotomized into longer (≥9 days) versus shorter (7>DGF<9 days) dialysis dependency, there was no difference in the slope of fibrosis progression in the multivariable mixed linear regression models.

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The strength of the paper, however, is in the large number of paired management biopsies from one center read by the local pathologists, which reduces the well known difficulties and variabilities in the scoring of fibrosis (8). Furthermore, the authors accounted for the possible effect of subclinical inflammation on fibrosis progression by adjusting their mixed model for the presence of tubulitis in the 4-month biopsy when available. Because the authors’ transplant center accepts a high rate of expanded criteria donors with a propensity for AKI before organ retrieval, the findings may not directly be applicable to DGF cases in standard criteria donors without AKI before procurement.

The good news from the paper by Heilman et al. (20) is that DGF does not seem to cause an acceleration of fibrosis in the first 2 years after transplantation. This observation is of critical importance to justify the continuously growing rate of donation after cardiac death donations, where a higher rate of DGF is observed but without penalization of midterm allograft function and probably morphology in recent eras (21). Of note, recent registry analyses from the Australia and New Zealand dialysis and transplant registry (ANZDATA) found the contrary (22). DGF was defined in these studies as only 3 days of post–transplant dialysis dependency, and only transplants until 2012 were included. In that era, the paper by Heilman et al. (20) is in line with the ANZDATA reports.

As also evidenced in the study by Heilman et al. (20), tubulointerstitial fibrosis is a highly prevalent progressive indolent process without proven therapeutic interventions. Therefore, future strategies will need to focus on prevention. The only realistic options are to minimize the alloimmune response to the graft. This can be accomplished by tolerance protocols that are currently only available for selected live donor recipients in few transplant centers worldwide and have their own specific unwanted effects. A likely more promising approach would be precise matching of donor and recipient HLA epitopes, in which multiple potential immunogenic sites of the HLA molecule are taken into consideration (23,24).

Other than the undoubted importance of HLA alloimmunity, non–HLA epitope matching may gain more attention in the near future. Opelz et al. (25) showed, in a landmark paper in 2005, that graft survival from HLA–identical sibling donors depended on the overall sensitization, suggesting that non-HLA alloimmunity is of non-negligible importance. We look forward to the findings from consortia recently assembled to study the effect of genome–wide donor and recipient incompatibilities on hard outcomes (26).

Disclosures

None.

References

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See related article, “Progression of Interstitial Fibrosis during the First Year after Deceased Donor Kidney Transplantation among Patients with and without Delayed Graft Function,” on pages 2225–2232.