

Chapter 7: Treatment of Chronic Allograft Injury

- 7.1: We recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes. (1C)**
- 7.2: For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C)**
- 7.2.1: For patients with CAI, eGFR >40 mL/min/1.73 m², and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTORi. (2D)**

CAI, chronic allograft injury; CNI, calcineurin inhibitor; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor(s).

Background

Historically, KTRs with gradually declining kidney allograft function associated with interstitial fibrosis and tubular atrophy (IF/TA) have been said to have ‘chronic rejection,’ or ‘chronic allograft nephropathy.’ However, these diagnoses are nonspecific and the Banff 2005 workshop suggested using ‘chronic allograft injury’ to avoid the misconception that the pathophysiology and treatment of this entity are understood (109). Causes of CAI include hypertension, CNI toxicity, chronic antibody-mediated rejection and others. Overall, death causes up to 50% of graft failures. However, of those who return to dialysis or require retransplantation, the most common cause is CAI, followed by acute rejection and recurrent primary kidney disease (110,111). Moderate to severe CAI is present in about one quarter of KTRs at 1 year after transplant, and in about 90% by 10 years (112–114). CAI is a diagnosis of exclusion characterized by the progressive reduction in graft function not due to recurrence of disease or other recognized causes. Histologically, CAI is defined by IF/TA (109,114). Other features may include subclinical rejection, transplant glomerulopathy or transplant vasculopathy.

Rationale

Graft function 6–12 months after kidney transplantation is an outcome reported in most RCTs of immunosuppressive medications. These are described in the relevant sections of these guidelines. Similarly, the use of other medications (antihypertensive agents, lipid-lowering agents, antiproteinuric agents) to prevent CAI or prevent the progres-

sion of CAI are also discussed in other sections of these guidelines.

Some causes of CAI may be reversible. Patients found to have acute rejection, BKV nephropathy or recurrent kidney disease, for example, may respond to appropriate treatments. Therefore, it is important that patients suspected of having CAI undergo biopsy, if possible. Most commonly, when there are no reversible causes of graft dysfunction, the biopsy will show IF/TA with or without other features consistent with CAI. In other words, the diagnosis of CAI is a diagnosis of exclusion. The roles of CNI toxicity, chronic antibody-mediated rejection and other immune and non-immune mechanisms of injury are unclear. The treatment of CAI has been controversial (115).

CNI withdrawal and/or replacement

Although there are a large number of uncontrolled studies describing the effects of withdrawing CNIs in KTRs with CAI (116), there are only two RCTs. In both RCTs, the CNI was replaced with an alternative immunosuppressive agent. In the ‘Creeping Creatinine’ study of 143 KTRs, MMF was substituted for CsA, and outcomes were reported at 12 months (117). There were no differences in mortality, graft loss, acute rejection, infection or blood pressure between the two groups. Those randomized to MMF had a small improvement in their creatinine clearance (+5.0 mL/min [+0.8 mL/s] vs. -0.7 mL/min [-0.01 mL/s]) at 12 months, but creatinine clearance was not measured in 20%, and the long-term importance of this outcome is uncertain. The ‘Chronic Renal Allograft Failure’ study replaced CsA with tacrolimus in 186 KTRs (2:1 randomization) with moderate CKD. Baseline creatinine was 220 μmol/L and outcomes were reported at 5 years (118). There was no difference in death, graft loss, acute rejection, treatment discontinuations, NODAT, hypertension, infections or cancer between the two arms. However, incident cardiac events favored tacrolimus. Over 5 years, serum creatinine increased in the CsA group by about 60 μmol/L compared with the tacrolimus group. Overall, the quality of evidence evaluating the effects of replacing a CNI in patients with CAI is low, and there is uncertainty regarding benefit–harm trade-offs (see Evidence Profile and accompanying evidence in Supporting Tables 42–44 at <http://www3.interscience.wiley.com/journal/118499698/toc>).

CNI replacement with mTORi

No RCTs have examined whether switching KTRs with established CAI from a CNI to an mTORi is beneficial. However, a RCT randomly allocated 830 KTRs with

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estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m² to continuation of CNI (N = 275) vs. converting to sirolimus (N = 555) (119). Patients were stratified into two groups based on eGFR 20–40 mL/min/1.73 m² (N = 87) and eGFR >40 mL/min/1.73 m² (N = 743). The Data Monitoring and Safety Board stopped the trial for patients with eGFR 20–40 mL/min/1.73 m² when the primary safety end point (acute rejection, graft failure or death at 12 months) occurred in 8 of 48 of sirolimus vs. 0 of 25 CNI patients (p = 0.045). In the stratum eGFR >40 mL/min/1.73 m², the primary end point (change in eGFR baseline

to 12 months) was not different in the two groups, but there was more proteinuria in the sirolimus group (119). Thus, this *post hoc* subgroup analysis suggested that converting patients with eGFR 20–40 mL/min/1.73 m² from CNI to sirolimus may be harmful, and that converting patients with eGFR >40 mL/min/1.73 m² may not be beneficial. However, the patients in this trial were not selected to have CAI *per se*, and it is possible that patients with CAI, preserved kidney function and low levels of proteinuria may still benefit from conversion. Additional study is needed.