BRIEF OVERVIEW OF RENAL SPARING IMMUNOSUPPRESSIVE REGIMENS POST-HEART TRANSPLANTATION

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Chronic kidney disease (CKD) is a common complication after heart transplantation\(^1\)\(^-\)\(^4\) increasing in incidence with time after transplant to 10.9% at 5 years\(^5\). A number of risk factors have been identified, these include use of calcineurin inhibitors, increasing recipient age, female gender, diabetes mellitus, hypertension, positive hepatitis C virus, need for renal replacement therapy post-operatively, renal function pre-transplant and deteriorating renal function within the first 3 months post-transplantation\(^2\)\(^,\)\(^4\)\(^,\)\(^6\)\(^,\)\(^7\). CKD is associated with increased mortality and morbidity with a relative risk for death with CKD of 4.55\(^5\). A recent UK survey reported the highest mortality risk was associated with a CKD stage 5 without dialysis compared to patients receiving dialysis (RR 8.54 vs 4.07\(^7\)).

Calcineurin inhibitors (CNIs) form the cornerstone of immunosuppressant regimens after heart transplantation\(^8\); however, they are associated with nephrotoxicity. The use of the newer ‘non-nephrotoxic’ immunosuppressants such as the proliferation signal inhibitors (sirolimus and everolimus), mycophenolate mofetil and the anti-CD25 (interleukin-2 receptor) monoclonal antibodies (basiliximab and dacluzimab) have allowed for a number of strategies which have shown potential to improve renal function in heart transplant recipients by allowing for CNI minimisation and even elimination\(^9\)\(^,\)\(^10\) - not all of which will be discussed here. The ultimate goal for such non-CNI based immunosuppression (or CNI minimisation) is to minimise or reverse renal damage but not at a price of increased acute rejection episodes or reduced patient survival.

Mycophenolate mofetil (MMF) inhibits purine synthesis in both T and B cells and is often used together with a CNI and corticosteroids post-transplantation. A number of studies including the IMPROVED trial have shown that switching from azathioprine to MMF followed by a reduction in ciclosporin levels in long-term cardiac transplant recipients could be achieved safely and lead to significantly lower serum creatinine\(^11\)\(^-\)\(^13\). While Hamour et al showed that it is possible to utilise MMF to decrease ‘early’ ciclosporin exposure safely, and hence the incidence of CKD stage 3a or worse was reduced\(^14\).

There are two proliferation signal inhibitors (PSI) or mammalian target of rapamycin (mTOR) inhibitors: sirolimus and everolimus, these inhibit T cell activation at a later stage to the CNIs. Sirolimus was the first available; everolimus has a much shorter half-life of 28 hours (vs 62 hours) allowing steady-state to be achieved earlier but is as yet not available commercially worldwide (e.g. in the UK it is available only on a ‘named-patient’ basis).

Early studies using the PSIs with full dose CNI have shown that although the PSIs were not thought to be inherently nephrotoxic, they will exacerbate CNI-induced renal dysfunction\(^15\)\(^,\)\(^16\). Subsequent studies have since used sirolimus
or everolimus with 'low dose' ciclosporin or tacrolimus with some benefit\textsuperscript{17-20}.

The Save The Nephron (STN) cardiac study looking at early post-transplant CNI elimination (at 12 weeks) with sirolimus and MMF was terminated prematurely due to an unexpectedly high incidence of grade IIIa biopsy proven acute rejection\textsuperscript{21}. However, 'late' CNI elimination with the use of a PSI together with MMF shows more promise\textsuperscript{22-27}, but the reports are somewhat variable. One study of five patients with severe renal impairment late after heart transplantation demonstrated accelerated renal failure\textsuperscript{28}. Alternatively, Gustaffson et al demonstrated that renal recovery from CNI CKD with sirolimus based immune-suppression correlated with shorter duration of CNI exposure and renal dysfunction\textsuperscript{29}. This has been confirmed in other studies, hence timing of the switch is important, and it is likely that residual renal dysfunction relates to irreversible structural kidney damage.

So when using a PSI do we minimise or eliminate the CNI in stable heart transplant patients with CKD? Gleissner et al compared low dose CNI with CNI-free sirolimus based immunosuppression and found that successful CNI elimination was more effective in improving renal function (in terms of estimated glomerular filtration rate) than CNI minimisation.\textsuperscript{30}

Unfortunately, sirolimus is often not well tolerated, often necessitating withdrawal due to its adverse effect profile which includes severe acne, mouth ulcers, myelosuppression, dyslipidaemia, infection as well as oedema, pneumonitis, impaired wound healing and increased proteinuria. Caution should be exercised with the use of sirolimus in patients with significant pre-existing proteinuria, the mechanism for this adverse effect is still not understood\textsuperscript{31}.

The interesting concept of a temporary 'CNI holiday' was reported in a small single centre study in patients with acute renal dysfunction. Basiliximab or dacluzimab temporarily replaced CNI therapy; basiliximab was given on days 1, 4 and then every 20 days, while dacluzimab was given every 7 days. Serum creatinine decreased significantly and was maintained at 3 months after re-introduction of the CNI. There were no acute rejection episodes, but, a number of patients required a further CNI holiday due to a new episode of acute renal dysfunction\textsuperscript{32}. However, prospective randomised clinical trials are required to confirm these preliminary findings.

There is no 'one size fits all' strategy for managing CNI-induced renal dysfunction, but these agents have given us new tools in our drug armamentarium to potentially improve patient morbidity and outcome.

**Disclosure statement:** The author has no conflicts of interest to disclose.

**References:**