Nephrotoxicity of ciclosporin A: short-term gain, long-term pain?

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Historical perspective

Ciclosporin (CsA) was first dosed in pilot renal transplant recipients at 25 mg/kg/day, based upon large animal experimental data [1], but was rapidly found to be nephrotoxic and the dose reduced to 10 mg/kg/day. Monotherapy at this dose was, however, found to provide inadequate immunosuppression [2] and a starting dose of 17.5 mg/kg/day was thus used in the early phase II/III of clinical studies [3,4]. This early experience changed the clinical practice of transplantation, since acute rejection became a more subtle clinical syndrome and a differential diagnosis of acute nephrotoxicity had to be considered for renal dysfunction. The therapeutic window of CsA, when used alone, proved too narrow and thus, triple therapy, including azathioprine and low-dose prednisolone was born in the late 1980s [5]. The histological picture of acute CsA nephrotoxicity was defined both in transplanted and native kidneys, with the widely agreed hallmarks being striped or diffuse interstitial fibrosis, nodular arteriolar hyalinosis and tubular calcification [6].

Acute nephrotoxicity

The functional impact of CsA nephrotoxicity appeared in the early formal randomized clinical trials [3,4,7] with impaired tubular function, higher serum urate levels and altered potassium handling. Blood pressure was increased and glomerular filtration rate (GFR) was reduced, but rapid recovery to control levels was observed after cessation of the drug. Synergistic toxicity with non-steroidal anti-inflammatory agents hinted at the vascular nature of the functional insult caused by CsA. Histological confirmation of CsA nephrotoxicity was seldom forthcoming in patients with acute rises in serum creatinine and clinicians learnt to rely for diagnosis, on an absence of the histological features of rejection together with a response to dose reduction. The reassurance that CsA nephrotoxicity was reversible—at least after 3 months of treatment—was encouraging, but the words of warning in those early papers with respect to uncertainty over reversibility in the longer term, went unheeded [7]. Short-term graft survival rates continued to improve throughout the 1990s and little attention was paid to the longer-term outcomes.

Chronic nephrotoxicity

The concern that chronic calcineurin inhibitor (CNI) nephrotoxicity was a major long-term problem should have been widely understood in the mid-1990s through...
the longer-term follow-up of trials of CsA treated patients [8,9]. Shorter-term pathology studies, such as that from a randomized trial of CsA and tacrolimus, also showed that 60–70% of patients in both groups had chronic histological damage at only 2 years after transplantation [10]. Definitive evidence that CsA nephrotoxicity impacted graft survival has been elusive, but two analyses of Australian data—both registry and long-term follow-up of an early randomised controlled study—clearly showed worse long-term outcomes in those maintained on CsA compared with those maintained without CsA [11,12].

The view developed during the late 1990s that ‘chronic rejection’ was an inappropriate term and that ‘chronic allograft nephropathy’ (CAN) was better. It became evident that multiple antecedent insults contributed to this histological picture, including ischaemia, acute and chronic allograft rejection and perhaps also CNI nephrotoxicity [13,14]. The true impact of CsA nephrotoxicity has thus been disguised over the past 15 years by a lack of data, lack of enquiry, lack of alternatives and therapeutic nihilism.

The histological studies that we commenced at Westmead in 1987 and reported in 2003 and 2004 [15–19] when added to other voices [9,20] threw an urgency into the debate over how to treat and avoid CAN [21]. It is now clear that chronic CNI nephrotoxicity causes long-term histological damage which is grossly underestimated by the renal functional change and which becomes largely irreversible by the time an elevated serum creatinine has alarmed either the clinician or the patient.

### Histological predictors

The early histological hallmarks of acute CNI nephrotoxicity [22] are usually present between 3 and 12 months after transplantation, and include transient de novo nodular arteriolar hyalinosis, striped cortical fibrosis, tubular microcalcification, juxta glomerular hyperplasia and isometric tubular vacuolization. The data correlating these histological changes with measures of CsA exposure have, however, been limited [17]. This picture is associated with the preceding episodes of acute CNI-induced renal dysfunction and is exacerbated by delayed graft function.

The chronic phase of CNI nephrotoxicity was seen in the Westmead histology study at a mean of 3 years after transplantation, increasing with time, until striped cortical fibrosis, severe circumferential and nodular arteriolar hyalinosis, and tubular calcification were present in the vast majority of patients who had used CsA for 10 years, 50% of whom had Banff criteria for grade III CAN [15]. While this knowledge is sufficient to destroy the hypothesis that striped fibrosis and arteriolar hyalinosis are simply the products of acute CsA overdosing, perhaps the most interesting correlates in this histology series are the impacts that these features have on subsequent glomerular sclerosis [19].

Interstitial fibrosis is followed by the development of glomerular sclerosis—and there was, in our data, several years’ delay between the observation of interstitial fibrosis and the development of significant glomerular sclerosis. Two-thirds of interstitial fibrosis occurred in the first year, as the combined result of ischaemia, CsA nephrotoxicity, severe acute rejection and other toxic agents. Subsequent fibrosis came largely from an insidious development of CsA nephrotoxicity in the form of striped fibrosis associated with arteriolar hyalinosis, or more rarely from persistent subclinical rejection. The amount of interstitial fibrosis, scored using the Banff schema for C1, seen at 1 year correlated significantly with the degree of early glomerular sclerosis in that same kidney later between 1 and 4 years [18], perhaps through the formation of atubular glomeruli. The second factor that correlated with glomerular sclerosis was the degree of arteriolar hyalinosis, further supporting the linkage between microvascular injury and ischaemic glomerulosclerosis [17]. If preventative action is to improve graft outcomes, then the histological data would suggest that we must put research effort into either preventing interstitial fibrosis or arteriolar hyalinosis, or de-linking the relationship between these events and glomerular sclerosis.

### Exacerbating factors

CsA dosing has been associated with the degree of histological change. The greater the dose, the more likely are the histological changes of both acute and chronic CNI toxicity. Acute arteriolar hyalinosis may resolve with dose reduction, though striped cortical fibrosis is an irreversible injury. In the Westmead study, a mean CsA dose above 5 mg/kg/day was associated with the development of permanent histological changes by 5 years after transplantation, though even those patients using lower doses mostly developed histological features of chronic CsA nephrotoxicity by 10 years [17].

In pivotal phase III studies of sirolimus and everolimus, both unwittingly demonstrated that the combination of this class of drugs with a CNI increased CNI nephrotoxicity [23,24]: the mechanism for which may be through a pharmacodynamic interaction which leads to intracellular accumulation of the CNI in tubular cells [25]. Interestingly, the histological impact of the withdrawal of a CNI was also demonstrated in the histology sub-study of the much-quoted trial of CsA withdrawal from a triple therapy regimen including CsA, sirolimus and corticosteroids [26]. This study showed an improvement in renal function and in the degree of tubular atrophy in the grafts in which CsA was withdrawn.
Table 1. Strategies to avoid long-term use of CNIs after renal transplantation

<table>
<thead>
<tr>
<th>Induction</th>
<th>0–3 months</th>
<th>Maintenance &gt;3 months</th>
<th>Comments and issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG</td>
<td>Srl/EvrL, MMF/Aza, Pred</td>
<td>Srl/EvrL, MMF/Aza, Pred [31]</td>
<td>Poor wound healing, hyperlipidaemia</td>
</tr>
<tr>
<td>II2r</td>
<td>Srl/EvrL, MMF/Aza, Pred</td>
<td>Srl/EvrL, MMF/Aza, Pred [29]</td>
<td>Poor wound healing, anaemia, hyperlipidaemia</td>
</tr>
<tr>
<td>C1H</td>
<td>Srl/EvrL, MMF/Aza, Pred</td>
<td>Srl/EvrL, MMF/Aza, Pred [30]</td>
<td>Infectious complications</td>
</tr>
<tr>
<td>Nil</td>
<td>CsA/Tacro, MMF/Aza, Pred</td>
<td>Srl/EvrL/MMF/Aza, Pred [27,28]</td>
<td>High early acute rejection rate, poor wound healing, anaemia, hyperlipidaemia</td>
</tr>
<tr>
<td>Nil</td>
<td>CsA/Tacro, Srl/EvrL, Pred</td>
<td>Srl/EvrL, Pred [26]</td>
<td>Acute rejection post conversion in 8–15%. Infectious complications</td>
</tr>
</tbody>
</table>

ATG, Anti-thymocyte globulin; II2r, basiliximab or daclizumab; C1H, alemtuzumab; CsA, ciclosporin; Tacro, tacrolimus; MMF, mycophenolate mofetil or mycophenolate sodium; Aza, azathioprine; Srl, sirolimus; Evrl, everolimus; Pred, prednisolone.

Strategies for avoiding chronic nephrotoxicity

The simplest strategy for avoiding CNI nephrotoxicity is clearly to avoid using the class of drugs, but this approach has often failed because alternative drugs of comparable immunosuppressive efficacy have not been available. This simple conundrum has lead to continuing attempts to use short-term CNI, for perhaps 3 months, and then to eliminate the CNI in favour of less nephrotoxic alternatives (Table 1). Structured meta-analysis of CsA elimination both in favour of azathioprine in combination with steroids, [27] and sirolimus and steroids [28] has demonstrated improved graft function, no impact on short-term graft survival, but a small increase in immediate post-elimination/conversion acute rejection rates, in the order of 8–11%. It may be the small immediate risk of acute rejection that is preventing widespread clinical implementation of such strategies.

An alternative approach involves avoiding CNIs entirely through a combination of sirolimus with mycophenolate mofetil, prednisolone and either monoclonal antibody to the II2 receptor [29] or Campath 1H [30]. This strategy may prove practical in the long term, but also has short-term consequences [29,30]. The most recently reported study of CNI-free therapy compared tacrolimus with sirolimus, both in combination with thymoglobulin, mycophenolate mofetil and corticosteroids in a predominantly low-risk living donor transplant population [31]. The excellent outcome in both groups (1 year: patient survival of 98 and 96%; graft survival 94 and 92%; and measured GFR 55 vs 55 ml/min/1.73 m²) underlines the difficulty of distinguishing long-term results from the short-term data. One year protocol biopsies showed similar degrees of interstitial fibrosis but more chronic vascular disease in the tacrolimus group, perhaps hinting at the potential for long-term differences.

In conclusion, long-term follow-up of clinical and histological data on patients either withdrawn from or never exposed to CNIs will be needed to demonstrate if the early pain is worth the long term gain.

Conflict of interest statement. JRC is an advisory Board and speaker panels for Novartis, Wyeth, Astellas and Roche.

References

Is liver analysis still required for the diagnosis of primary hyperoxaluria type 2?

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Keywords: glyoxylate reductase; GRHPR; primary hyperoxaluria type 2 (PH2)

The primary hyperoxalurias (PH) are inherited disorders of glyoxylate metabolism, leading to endogenous oxalate overproduction and the inevitable precipitation of calcium oxalate, leading to renal stones and/or nephrocalcinosis and renal failure. Type 1 PH (PH1) is caused by deficiency of alanine: glyoxylate aminotransferase (AGT), while the type 2 disease (PH2) is due to lack of glyoxylate reductase/ hydroxypropionate reductase (GRHPR). While AGT is liver-specific, GRHPR is ubiquitously expressed although predominantly in the liver [1,2].

As the presenting symptoms of both the diseases are very similar, but with a slightly better prognosis for PH2, it is important to make a correct diagnosis to enable appropriate management decisions to be made including choice of liver–kidney or kidney-only approaches.