Renal hypoperfusion as the primary cause of cyclosporin-induced nephropathy

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Introduction

In clinical practice a more extensive use of cyclosporin A (CsA) as an immunosuppressive agent is limited by the appearance of renal impairment, commonly designated ‘CsA nephrotoxicity’, a progressive and irreversible structural damage to the kidney associated with chronic administration of the drug [1].

On the other hand, in the last few years consistent evidence has been collected about a primary and reversible renal haemodynamic effect after short and long-term treatment with CsA. Indeed, renal vasoconstriction has been observed after both acute and chronic CsA administration; in these conditions renal function has been demonstrated to be strictly dependent on the CsA dosage and the basal state of renal dynamics. Taken together these data offer important clinical implications for treating patients with CsA.

Renal dysfunction induced by acute CsA administration

Evidence of renal vasoconstriction

Acute administration of CsA in humans leads to a functional renal impairment; indeed, either when administered in high (12 mg/kg b.w.) or low (4 and 5 mg/kg b.w.) doses, CsA induces a decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF) (Figures 1 and 2), and an increase in filtration fraction (FF) (Figure 1), and in renal vascular resistances despite no variation in blood pressure [2,3]. All these haemodynamic changes are associated with sodium retention (Figure 1). Vasodilating doses of dopamine (1–2 µg/kg b.w./min) counteract these CsA effects, thereby re-establishing a normal RPF and GFR (Figure 1) [2]; these results further support the hypothesis of the exclusive role of renal vasoconstriction in the genesis of renal dysfunction following acute CsA administration.

These data obtained in humans are in agreement with the observed changes in the renal parenchyma in animal models and in cases of human CsA nephrotoxicity.
Renal dysfunction by cyclosporin

Fig. 2. GFR (clear columns) and RPF (dashed columns) in basal conditions (Basal) and after oral administration of 3, 4, and 5 mg/kg b.w. of cyclosporin (CsA) in healthy subjects (n=7). *P<0.01 versus Basal.

with those observed in rats by micropuncture technique which demonstrate a marked glomerular vasoconstriction in both pre- and postglomerular vessels and in glomerular capillaries (as suggested by the decreased glomerular ultrafiltration coefficient, Kf) and the complete reversion of these changes by dopamine infusion [4].

Dosage as critical factor of renal vasoconstriction

In humans, a low dosage of CsA (3 mg/kg b.w.) does not significantly decrease RPF or GFR despite serum CsA being greater than the immunosuppressive threshold (Figure 2) [3,5]. Similarly, in rats the detrimental effects of CsA on renal function are strictly dose dependent and there is a critical CsA dosage less than which both RPF and GFR are not reduced in presence of immunosuppressive concentrations of CsA [6].

Basal renal dynamics and CsA-induced nephropathy

If CsA acts as a powerful renal vasoconstrictor, its deleterious effects will be more severe in some pathophysiological conditions, such as hypovolaemic states, in which the maintenance of a normal GFR depends on a new unstable equilibrium between renal vasoconstrictors and vasodilators. Indeed, it has been demonstrated that the decrease of GFR observed after a single oral bolus of CsA (10 mg/kg b.w.) is greater in patients with nephrotic syndrome (-40%) than in healthy subjects (-15%); nephrotic patients had low basal values of blood volume and renal plasma flow despite a normal basal value of GFR and CsA values similar to those of healthy subjects (Figure 3) [7]. These data confirm the hypothesis that in the presence of pre-existing renal hypoperfusion, CsA further reduces RPF, causing a disproportionate decrease of GFR (Figure 3). Thus, it is reasonable to believe that all clinical conditions characterized by hypovolaemia and/or renal hypoperfusion (i.e. oedematous syndromes, osmotic diuresis in patients with diabetes mellitus, renal artery stenosis, and diuretic therapy) or by blockade of the compensatory prostaglandin-

induced renal vasodilatation (e.g. administration of non-steroidal anti-inflammatory drugs) represent a worsening factor for renal function impairment during CsA therapy, even when GFR is initially normal.

Renal dysfunction induced by chronic CsA treatment

Evidence of renal vasoconstriction

Prolonged administration of CsA also induces functional alterations in renal haemodynamics. Two months of immunosuppressive therapy with CsA in patients affected by psoriasis result in a significant decrease in RPF and GFR associated with increased renal vascular resistances in absence of any change in blood pressure; after withdrawal of CsA all these functional alterations return almost to basal values [8]. Studies in patients treated 1 month with CsA (5 mg/kg b.w./day) for psoriasis, have shown that chronic oral administration of misoprostol (100 µg twice a day), a vasodilatory prostaglandin E1 analogue, completely reverses CsA-induced renal hypoperfusion despite serum CsA levels comparable to those of patients treated with CsA alone (Figure 4) (unpublished data). Other studies have demonstrated that fenoldopam, a dopamine-like vasodilator, acts as an effective renal
vasodilator in kidney transplant patients on CsA by increasing RPF and decreasing blood pressure [9].

Similarly, micropuncture studies in rats have demonstrated that after medium-term administration of CsA the observed reduction of GFR depends on a marked increase in preglomerular resistance and the consequent decrease in glomerular capillary pressure; the renal impairment is completely reversed by CsA withdrawal [10]. Moreover, the changes in renal haemodynamics observed after chronic CsA administration correlate with the degree of the tubular vacuolization in a time-dependent fashion, and after CsA withdrawal the recovery of renal function is associated with the absence of tubular damage [10].

**Dosage as critical factor of renal vasoconstriction**

In the treatment of patients with psoriasis, the tapering of CsA dosage (from 5 mg/kg b.w./day to the complete withdrawal after 2 months) and the consequent parallel decrease in CsA blood concentrations are associated with a decrease of renal vasoconstriction, mirrored by the increase in RPF and GFR (Figure 5) [8]. It is also important to note that in agreement with acute findings a dosage of 3 mg/kg b.w./day of CsA for 2 months does not decrease GFR [11].

That such a low dosage is critical to avoid progressive CsA-induced nephropathy has been observed also after longer treatments. Indeed, a stability of renal allograft function in conjunction with a CsA maintenance dose of about 3 mg/kg b.w./day has been demonstrated up to 5–8 years after transplant in a consistent group of bone-marrow, heart, and kidney recipients [12–14]; these observations indicate that long-term administration of CsA does not have deleterious effects on renal function if low doses are used. As a further support to the important linkage existing among CsA dosage, RPF, and GFR, it has been shown that progressively lower doses of CsA in transplanted patients studied for an average of 2 years were inversely correlated with RPF and associated with a stable GFR [15]. Finally, as shown in Figure 5, a longitudinal study in CsA-treated patients, examined at 2 and 4 years after transplantation, demonstrates that the reduction in CsA blood levels allows renal plasma flow to improve and GFR to be preserved [15].

Thus, taken together, these findings underline the crucial role of a gradual CsA dosage reduction in preserving renal function, and indicate that CsA renal dysfunction is dose dependent and still partially reversible after several years of therapy.

**Basal renal dynamics and CsA-induced nephropathy**

In 1-year post-transplant patients undergoing CsA therapy, a modest intravascular volume depletion, induced by dietary sodium restriction and frusemide administration, leads to a significant decrease in GFR, promptly reversed by intravenous saline infusion. In contrast, the same manoeuvre does not modify GFR in azathioprine-treated patients [16]. Therefore, during long-term CsA therapy, volume depletion predisposes to a reversible worsening of renal function. Interestingly, CsA-treated patients exhibit a greater decrease in fractional sodium excretion after hypovolaemia; this tendency of CsA to cause sodium retention is due to renal vasoconstriction and, most probably,
accounts for the frequent development of volume-dependent hypertension. In fact, sodium restriction significantly decreases the mean arterial pressure in hypertensive CsA-treated transplanted patients, and similarly to GFR, changes in the volume status remain without any effect on arterial pressure in hypertensive transplanted patients treated with azathioprine [17].

**Clinical implications**

In conclusion, CsA-induced nephropathy is functional and reversible, depending on a primary renal hypoperfusion. Glomerular vasoconstriction plays a critical role also during prolonged CsA administration, being probably responsible for the development of the structural damage. Therefore in the use of CsA some fundamental guidelines should be followed in order to preserve renal function:

1. CsA should be used at low dosage or, at least, the dose should be gradually tapered to 3 mg/kg/day, an immunosuppressive dose that does not modify renal haemodynamics.
2. Patients should be kept on a sodium-restricted diet to prevent hypertension.
3. Hypovolaemia and/or renal hypoperfusion should be avoided by removing the causes and limiting the use of diuretics and/or non-steroidal anti-inflammatory agents.
4. Renal vasodilating agents, such as dopamine analogues or misoprostol or, as recently suggested, calcium-channel blockers [18], should be given with CsA to counteract the vasoconstrictive and hypertensive effects of CsA.

**References**