Nephrotoxicity of calcineurin and mTOR inhibitors

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Introduction

Cyclosporine A (CSA) was introduced into clinical practice in the early 80s resulting in a large decrease in the incidence of acute rejection in renal transplantation and increasing solid organ transplant graft and patient survival to unparalleled levels. Subsequently, its use was extended to bone marrow transplant immunosuppression and to the treatment of a variety of autoimmune diseases refractory to conventional therapy, again with noteworthy efficacy [1-6]. The subsequent development of CSA self-emulsifying formulations improved bioavailability, decreased inter- and intra-patient variability and allowed more precise drug dose-tailoring [3, 7]. More recently, generic CSA brands have become available, decreasing treatment costs substantially. The combination of efficacy, accumulated experience and decreasing cost makes CSA still widely used in the clinical practice, and large numbers of patients are currently exposed to this drug.

In 1989 tacrolimus (TAC), a second calcineurin inhibitor was approved for clinical use [8]. Tacrolimus has an immunosuppressive effect approximately 100 times more potent than CSA and early clinical trials demonstrated that TAC was effective in reversing refractory acute rejection in renal, liver and heart transplantation. Subsequently, this drug was shown to be at least as effective as CSA in the primary immunosuppression schedules for solid organ and bone marrow transplantation and, similar to CSA, has proven to be a valuable alternative in the treatment of autoimmune diseases [3, 9-11]. Because the facility of drug monitoring by trough levels, less cosmetic side effects and a putative better profile in preventing acute rejection, TAC use has increased significantly and in fact, it has become the calcineurin inhibitor of choice for the prevention of rejection in solid organ transplantation in the majority of centers.

Both drugs inhibit interleukin-2 gene transcription and the transition of T lymphocytes from the G0 to G1 phase of the cell cycle. They bind to cytoplasmic immunophilins, cyclophilin for CSA and FK-binding protein (FKBP12) for TAC. The immunosuppressive drug-immunophilin complex reduces calcium signaling, blocking a calcium dependent enzyme, calcineurin phosphatase, responsible for the nuclear translocation and dephosphorylation of the cytosolic nuclear factor of activating T lymphocytes (NF-AT-c). NF-AT-c regulates the transcription of genes responsible for several cytokines, including interleukin 2 [3].

The most important side effects for both drugs are kidney-related: acute and chronic renal dysfunction, hemolytic-uremic syndrome, hypertension, electrolyte disturbances (hyperkalemia, hypomagnesemia and hypocalcemia), renal tubular acidosis and defects in urinary concentrating ability. Among them, nephrotoxicity is considered the most significant and limiting adverse effect. Interestingly, sirolimus which reduces interleukin 2 production without blocking calcineurin has a different pattern of nephrotoxicity [12]. When calcineurin is inhibited, the interleukin 2 gene is not the only gene which has its transcription impaired. Actually, the list includes genes for other interleukins, interleukin 2 receptor, nitric oxide synthase, transforming growth factor β (TGF-β), endothelin, collagen I and IV and bcl-2, responsible for protein Bcl-2, which is likely implicated in cellular protection against apoptosis [13]. It is possible that calcineurin inhibition at the same time that it blocks immune cell-mediated reaction against the transplanted tissue triggers a sequence of undesirable events that will eventually lead to renal injury [13]. The development of selective calcineurin inhibitors that disrupt genes transcription of particular genes without affecting the others may clarify this important issue [14].

Calcineurin inhibitor nephrotoxicity presents as two distinct forms of renal injury. Acute nephrotoxicity is a dose-dependent, hemodynamically mediated disorder, not accompanied by particular or permanent structural changes which is reversible with decrease or discontinuation of the offending drug. On the other hand, calcineurin inhibitor-induced chronic nephrotoxicity is an insidious lesion, characterized by an irreversible and progressive renal interstitial fibrosis, which may cause important impairment in renal function and even stage 5 chronic kidney disease.