

## TRANSPLANTATION

# Epithelial-to-mesenchymal transition: a biomarker of ciclosporin-induced nephrotoxicity

The degree to which use of calcineurin inhibitors is associated with the development of interstitial fibrosis and tubular atrophy is a matter of debate. A retrospective analysis of a randomized, controlled trial (RCT) now shows that the intensity of expression of two markers of epithelial-to-mesenchymal transition (EMT)—vimentin and  $\beta$ -catenin—can identify ciclosporin-treated kidney transplant recipients at risk of fibrogenesis and a decline in graft function. “EMT is a generic response of the epithelium in the context of injury, and we hypothesized that renal grafts that were chronically injured by ciclosporin would exhibit EMT-like phenotypic changes,” says investigator Marc Hazzan.

The RCT included 108 kidney transplant recipients on ciclosporin, mycophenolate mofetil (MMF) and prednisone. At 3 months after transplantation, patients were gradually withdrawn from either

MMF or ciclosporin. EMT scores were assessed in 68 patients at month 3 and month 12 after transplantation.

“...the phenotypic changes observed in tubular cells reflect a state of chronic injury...”

In the patients who continued on ciclosporin (ciclosporin group), mean vimentin and  $\beta$ -catenin scores increased significantly from month 3 to month 12, whereas they remained stable in the MMF group. When episodes of biopsy-proven acute rejection (which can trigger EMT) were excluded, vimentin and  $\beta$ -catenin scores still progressed between month 3 and month 12 in the ciclosporin group, whereas they decreased in the MMF group. The interstitial fibrosis score at month 12 was higher in patients who were EMT-positive at month 3 than in

those who were EMT-negative. Kidney recipients who continued on ciclosporin and exhibited severe EMT (score  $\geq 2$ ) at month 3 had a significant decrease in glomerular filtration rate up to 4 years after transplantation, whereas those who stopped ciclosporin did not.

“Ciclosporin withdrawal considerably abated the negative predictive value of EMT at 3 months,” says Hazzan. “Our data indicate that the phenotypic changes observed in tubular cells reflect a state of chronic injury, and that withdrawal of ciclosporin is a valid option at the bedside to attenuate injury and halt fibrogenesis in the graft.”

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