Nature Reviews Urology | Published online 9 Aug 2016; doi:10.1038/nrurol.2016.149

Glowimages/Getty

TRANSPLANTATION

GoCAR — on the road to reduced allograft loss

Data obtained during the Genomics of Chronic Allograft Rejection (GoCAR) study and reported in *The Lancet* have revealed a 13-gene set that can be used to independently predict the development of fibrosis 1 year after kidney transplantation. This observation means that kidney transplant recipients who are at risk of allograft loss could be identified before irreversible damage has developed, and enable steps to be taken to slow, stop, or reverse the fibrotic process.

The GoCAR study is a prospective, multicentre investigation conducted at five sites in the USA and Australia to study whether prediction of chronic allograft injury is possible using differential gene expression. Renal allograft of two biopsy samples were taken at 0, 3, 12, and 24 months after transplantation — one was analysed histopathologically and the other genomically. Overall, 204 patients had a biopsy sample taken at 3 months post-transplant, 159 samples were used as the discovery set and the remaining 45 were used as the validation set.

Genes that were significantly associated with the Chronic Allograft Damage Index score at 3 months and 12 months (CADI-3 and CADI-12) were identified using Spearman rank correlation. Notably, genes associated with CADI-3 were related to alloimmunity, and those associated with CADI-12 were related to programmed cell death or apoptosis. An optimal set of 13 genes from this original correlation analysis was then identified.

This 13-gene set was able to differentiate samples with high CADI-12 scores from those with low CADI-12 scores with an area under the curve (AUC) of 0.967. Cross validation of the gene set resulted in an average sensitivity of 81%, specificity of 79% and AUC of 0.889. In the validation cohort, the gene set differentiated high CADI-12 scores from low CADI-12 scores with an AUC of 0.866.

The 13-gene set also accurately predicted fibrosis based on Banff score with an AUC of 0.922 and on diagnosis with an AUC of 0.923. Furthermore, the gene set predicted the occurrence of high or low estimated glomerular filtration rate (eGFR) at 12 months (AUC 0.872) and 24 months (AUC 0.928).

Multivariable analysis showed that the gene set was better at predicting CADI-12 scores than baseline clinical variables alone or in combination with pathological variables and eGFR obtained at 3 months after transplant. Moreover, the gene set could accurately predict which patients would or would not experience CADI score progression at 12 months (AUC 0.916) and 24 months (AUC 0.845), and also those patients at risk of time-dependent allograft loss (AUC 0.844 by 2 years).

These data show that a new 13-gene set from allograft biopsy samples taken 3 months post-transplant can predict the development of fibrosis and risk of allograft loss. Potentially, this gene set could be used clinically to identify patients likely to need therapeutic intervention before fibrosis develops.

Louise Stone

ORIGINAL ARTICLE O'Connell, P. J. *et al.* Biopsy transcriptome expression profiling to identify kidney transplants at risk of chronic injury: a multicentre, prospective study. *Lancet* http://dx.doi.org/10.1016/S0140-6736(16)30826-1 (2016)