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P216 -A clinical, immunogenetic and immunophenotyping re-evaluation of the risk factors for and consequences of CMV disease following kidney transplantation, with a focus on cardiovascular sequelae

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Although data demonstrating an adverse effect of post-transplant CMV disease in regard to patient and graft outcome exists, ongoing re-evaluation is required as clinical, antiviral and immunosuppression strategies change and improve. The primary purpose of this study was to assess the adverse consequences of CMV disease in this setting; the secondary aims were to hypothesise regarding the potential mechanism of this effect, and to evaluate the role of HLA-Cw7 in the risk for CMV disease, as this allele has shown association with viral disease in other settings.

We analysed the demographic and clinical characteristics of 569 patients transplanted 2007-2011 under a standardised tacrolimus/mycophenolate immunosuppression regimen, and with median follow-up of 10 years. Data was captured in the prospective departmental database, and in the organisation's electronic record. Data regarding mortality and hospitalisation (and cause) were cross referenced with robust data from the Office of National Statistics (ONS).

Antiviral prophylaxis (valganciclovir) was administered to CMV-seronegative recipients of CMV-seropositive donors. CMV disease was diagnosed when fever was accompanied by detectable CMV viraemia, with or without tissue-invasive disease. All cases were treated with immunosuppression reduction and simultaneous oral valganciclovir or intravenous ganciclovir (for more severe disease)

There were 105 cases of CMV disease. Unsurprisingly, the dominant risk factor was CMV serostatus of donor and recipient, with D+/R- and D+/R+ patients experiencing greater CMV rates. However, and of interest, recipient (but not donor) HLA-Cw7 status also represented a risk factor for CMV disease, with a protective effect seen and persisting on multivariable analysis ($p<0.05$).

No effect of CMV disease upon graft survival was observed. However, there was a significant effect seen in regard to patient survival, with mortality rates of 13/105 (12.4%) and 30/464 (6.5%) in those experiencing and not experiencing prior CMV disease respectively ($p=0.03$), an effect which persisted on multivariable analysis adjusted for donor and recipient characteristics and post-transplant events.

The causes of death were equivalent between CMV disease and no-disease groups in regard to infection and malignancy. However, a disproportionate increase in cardiovascular mortality was seen in patients experiencing prior CMV disease (8/13 deaths versus 7/30; $p=0.01$), an effect which persisted in multivariate analysis also adjusted for recipient cardiovascular risk. Data from ONS supported these findings, showing increased hospitalisation rates for cardiovascular disease in patients experiencing CMV disease, even when excluding deaths.

We raise the hypothesis that this effect may be mediated by atypical, cytotoxic CD4 CD28 null cells, which demonstrate CX3CR1-dependent endothelial homing and NKG2D-associated endothelial toxicity, and which have shown associations with cardiovascular disease in the general population. In a separate, prospective

study of 100 transplant patients, we observed increased frequencies of such phenotyped cells (peripheral blood flow cytometry) as a component of total CD4 cell frequency in patients (n=12) developing cardiovascular events following transplantation.

In summary, we maintain that CMV disease remains a relevant risk factor for adverse patient outcomes in the current era, and offer a potential cellular mechanism to explain this finding. We also highlight novel data suggesting a role for HLA-Cw7 in protection from infection.