An explanation for post transplant late onset disease associated with CMV prophylaxis

Cytomegalovirus (CMV) is such an important pathogen after solid organ transplantation that all transplant centres should have protocols in place to reduce its impact.(1) These are based on one of two strategies; prophylaxis or pre-emptive therapy.

In the former, patients are given valganciclovir immediately after transplant, often as soon as they can take oral medication, and continued for a fixed time with randomised controlled trials supporting 100 days or 200 days of therapy.(2) This strategy is effective while patients are taking the medication, but some develop late-onset CMV disease once prophylaxis is stopped.(3) This disease is difficult to treat, often fails to respond to standard dose intravenous ganciclovir, is associated with strains of CMV resistant to ganciclovir, often requires foscarnet therapy and resistance to foscarnet may also develop.(4) It is as if the immune system is making a poor contribution to the control of CMV so on-going replication in the presence of ganciclovir or foscarnet selects for resistance against one or both of these drugs. The problem is common enough to allow substantial numbers of patients to be available for a phase 2 randomised controlled trial of maribavir(5), with a phase 3 trial currently following up the encouraging results seen so far (NCT02931539).

For the strategy of pre-emptive therapy, patients are monitored post-transplant with serial samples of blood and only given valganciclovir if their viral load has the potential to reach the high levels associated with end-organ disease.(6-8) The treatment is stopped once an individual's blood PCR result has given undetectable results for CMV DNA on two consecutive samplings as a way of reducing selection for resistant strains.(8, 9) Monitoring continues and some patients may need treatment for a second, or third, episode. However, eventually, the immune system of the patient manages to control CMV so that viraemia is no longer detectable and their risk of CMV end-organ disease declines back to baseline.

We thus have two strategies that can each significantly reduce the risk of CMV end-organ disease post-transplant, although neither strategy is perfect.(1) Proponents of prophylaxis emphasise the importance of being able to give a prescription to patients leaving the safety and expertise of a transplant centre to travel home to isolated communities without access to sophisticated laboratory services able to test for CMV DNA by PCR. Proponents of pre-emptive therapy emphasise the importance of minimising the selection for resistant strains and the "personalised medicine" aspect of treating patients as individuals using a pharmacodynamic readout of how well their immune system is controlling CMV. More than a decade ago, I persuaded two eminent colleagues to argue for and against these two strategies in a debate published in *Reviews in Medical Virology* and the points made on both sides have stood the test of time.(10, 11) However, one of the suggestions made(11) as an explanation for the paradoxical appearance of

late onset disease only after drugs with high potency against CMV became available is now supported by evidence from a recent publication.(12)

The problem of late onset disease is seen largely in CMV seronegative recipients who receive an organ from a seropositive donor.(4) Under these circumstances, the immune system of the recipient is attempting to mount a de novo response to a new antigen in the presence of immunosuppressive drugs. Many of these block the serial divisions of B-cells and T-cells required to give high affinity effectors able to control viral replication, so it is easy to see why transplant patients generally have a poor response to CMV. Superimposed on this, the lymphocytes of patients receiving prophylaxis may experience reduced antigen presentation as they divide serially in response to stimulation by the virus acquired initially from the donor.(13) The result may be creation of an immune response to CMV that is suboptimal. This would not be apparent while the patient was taking prophylaxis but, once the drug was stopped, the patient would be at risk of being unable to control CMV replication in the future.

This possibility has now been tested using samples from a clinical trial (to be reported separately) that randomised liver transplant patients to be managed by prophylaxis or by pre-emptive therapy.(12) Neutralising antibodies and multifuctional T-cells (defined as those producing more than one of interleukin 2, interferon gamma or tumour necrosis factor alpha when stimulated with CMV antigens) were assessed.(12) The results show significantly superior immune control of CMV after pre-emptive therapy when measured 3 months post-transplant.(12) Specifically, neutralising antibodies and multifuctional CD8 T-cells stimulated with peptide libraries from phosphoprotein 65 or immediate early 1 proteins of CMV showed major differences. In contrast, no difference was seen for multifuctional CD4 T-cells stimulated with the same peptide libraries. Thus, the impairment after prophylaxis affected both cell-mediated and humoral arms of the immune system. CD8 T-cells and B-cells seem to be more important than CD4 T-cells.

These results are important, because they address the relative merits of the two strategies used at present and help explain why late-onset disease only became apparent after prophylaxis was introduced. It will be important to determine if prophylaxis with drugs other than valganciclovir, eg letermovir, have the same effect after solid organ transplant. They also provide valuable information on which immune responses may be protective against CMV post-transplant, thereby providing a target for novel vaccines to aim for if we wish them to protect transplant patients.(14) Finally, they draw attention to the fact that the risk borne by CMV seronegative recipients can be reduced if they mount an effective immune response against this virus and should encourage the conduct of more randomised controlled trials to give prototype CMV vaccines pre-transplant as a way of controlling CMV viral load post-transplant.(14) A new phase 2 randomised controlled trial is currently underway in renal transplant patients with a novel vaccine based on a backbone of lymphocytic choriomeningitis virus and the results are awaited with interest (NCT03629080).

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