Poor responses to Pneumococcal vaccination in CKD patients – do we need to talk about cytomegalovirus again?

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As the current SARS-CoV-2 pandemic illustrates only too well, vaccination and immunological memory represent the most effective way of protecting a population from infectious diseases. Patients suffering with chronic kidney disease (CKD) account for around 8% of the population – a non-infectious disease that becomes more prevalent with age. CKD patients have an increased risk of infection, including pneumococcal disease, and thus vaccination is considered an important protective measure. However, previous studies have suggested that vaccine responsiveness is variable in CKD patients despite retaining good responses against some historical antigens. In the current study by Wall et al, the authors present data that argues in aging populations CKD itself is not a predictor of poor vaccine responses. Instead, they identify that latent human cytomegalovirus (HCMV) infection and prior exposure to PPV23 (Pneumovax23 vaccine) are predicted risk factors in their cohort.

HCMV establishes lifelong infections of the host with over 50% of the world's population predicted to be infected. HCMV infection of healthy/immunocompetent individuals is usually subclinical with symptoms rarely observed. In contrast, the significant disease burden in immune-suppressed organ transplant and HIV patients, and congenital infection means HCMV retains highest priority status for a vaccine [1, 2].

Although HCMV infection/reactivation is considered asymptomatic in healthy people it has a profound impact on the immunological repertoire in those individuals. Cellular immunity against HCMV can be upwards of 20% of the total T cell compartment as responses against HCMV accumulate over time. Pertinently, this HCMV driven expansion has been suggested to promote an increase in T cell populations with reduced functionality. This concept of HCMV associated immune-senescence or immune-aging has been postulated as one factor explaining poorer vaccine responses with age, although this is contested [3]. One over-arching issue with any longitudinal studies has always been identifying the time and thus duration of HCMV infection in the host and hence determining the long-term effect of chronic HCMV infection/reactivation on the immune response. Thus both HCMV seroprevalence and length of infection could therefore be important confounders in vaccine studies accounting for reported differences.

Wall et a investigated the humoral immune response against T cell dependent (TD- influenza) and T cell independent (TI – pneumococcal) vaccines. Responses against both vaccines were reduced but independent of CKD status. Previous studies suggest HCMV serostatus impacts on responses to TD vaccines and is linked to the profound impact HCMV has on the T cell compartment [3]. A caveat of the Wall study is that patients were recruited from multiple seasonal influenza vaccination schedules. Whilst unlikely to be a source of major variation it remains a consideration that differences in the composition and preparation of the seasonal influenza vaccines is a potential confounder.

A major new observation of the paper is the potential impact of HCMV seropositivity and previous PPV23 exposure on the development of humoral responses following vaccination with PPV23. Although the precise mechanism by which HCMV could impact TI vaccine responses remains unclear, this could be mediated through dysfunction of a number of different pathways supporting plasma cell differentiation/survival. Long lived memory B cells responses to TI vaccines are dependent on T follicular helper (TfH) cells and cytokine signaling from neighbouring immune cells, promoting B cell survival and driving antibody class switching. An important source of these cytokines are macrophages. Given that HCMV latency and reactivation is intimately associated with the mono-myeloid lineage this could have profound effects on macrophage function [4]. However, the frequency of latently infected myeloid cells in a healthy individual is predicted to be less than 0.01% [5], implying infection of a small minority of macrophages can exert a major function. Another possibility is the direct effect of latent HCMV infection on Tfh populations and/or through additional effects on other components of innate immunity. For instance, HCMV infection/reactivation has a significant effect on the differentiation and function of NK cells [6], which have been shown to regulate CD4 T cells and TFh activity thereby shaping the breadth and magnitude of antibody responses and generation of broadly neutralizing antibodies [7]. It remains plausible that individuals with poorer responses experience more frequent episodes of low level active HCMV replication. This will require testing of longitudinal sera samples for evidence of HCMV viraemia, as HCMV antibody levels may not be a sufficient surrogate marker of HCMV burden.

An important factor that cannot be addressed in such a study design is the cumulative impact of long-term chronic HCMV infection on the immune response. Although it is predicted that most people who are HCMV positive acquired HCMV during childhood the time of acquisition, particularly in countries with higher socio-economic status, is becoming later. Thus, within the HCMV effect reported it may be that those living with a persistent HCMV infection longer make a greater contribution to the phenotype reported in this current study. Given the potential timeframe of infection (upwards of 60 years) dissecting the details of this is likely to involve animal models of CMV infection where time and duration of infection can be standardized. However, whether short lived animal models can truly capture the effects of this long-term interaction of HCMV with the host immune system is not fully understood and so these models would have to be used cautiously. We also cannot rule out viral (and potentially host) genetics – it is possible that some strains of HCMV have a greater effect than others in shaping the heterogeneity and functional responses of immune cell populations. Again, the numbers required to power such a study is beyond the scope of the publication by Wall and colleagues.

The study also suggests prior pneumococcal vaccination may be linked with poorer responses. Vaccination against the debilitating disease associated with pneumococcal infections is important for multiple vulnerable populations, including immunocompromised individuals. HIV patients are a particularly high-risk group for invasive pneumococcal disease, despite the availability of effective antiretroviral treatment ART [8]. With a growing population of ageing HIV+ individuals, the majority of whom are co-infected with HCMV, these findings have important implications. The observation that repeat PPV23 vaccination becomes less effective is consistent with reduced responsiveness or immune tolerance to repeat polysaccharide vaccination reported by previous studies. These attenuated responses to secondary vaccination could be due to a variety of factors acting alone or in combination, leading to an overall depletion of the B cell memory pool. However, the exact mechanisms behind the observed long-lasting blunted responses remain unclear and need to be better defined in future studies, interrogating multiple components of innate and adaptive immunity. These findings, none the less, argue for a more nuanced approach with different pneumococcal vaccine preparations to optimize responses and protection against disease in older

and high-risk populations. In contrast to HCMV infection, the timing of vaccination will be known allowing for the impact of the vaccine schedule to be addressed.

A remaining question is how to best apply this knowledge. Understanding the impact of chronic viral infection on immune function is still an under-appreciated but important topic of investigation. Greater understanding of the pleiotropic effects of chronic HCMV infection on immunological responses could argue for the implementation of a broader HCMV vaccine strategy (once one is developed) beyond immediate high-risk groups for HCMV infection (e.g. women of child-bearing age and transplant patients).

In summary what this study highlights again is the under-appreciated impact of HCMV infection on host immunity and exemplifies the long term threat chronic viral infections pose to aging populations.

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