**Background**

Infection is the leading cause of death in ANCA-associated vasculitis (AAV). Accumulation of CD4+CD28null T-cells, driven by asymptomatic reactivation of cytomegalovirus (CMV), is associated with increased risk of infection and mortality. This study aimed to investigate whether CMV infection impairs the immune response to heterologous antigens in AAV.

**Methods**

Thirty-six CMV-seropositive AAV patients in stable remission were vaccinated with a T-cell dependent 13-valent pneumococcal conjugated vaccine (PCV-13). Serotype specific IgG titre was measured before and 4 weeks after vaccination. Protective response was defined by antibody titre >0.350 g/mL for ≥8/12 serotypes measured. Mean antibody response ratio (post/pre-vaccination titre; ARR) across all serotypes measured was used as a total measure of immune response. The host immune response to CMV was determined by enumerating CD4+CD28null T-cells, and CD4 T-cells secreting IFN- following CMV lysate stimulation, immediately prior to vaccination by flow cytometry. Asymptomatic CMV reactivation during the 6 months preceding vaccination was measured in urine monthly by quantitative PCR. Pre-vaccination peripheral blood mononuclear cells were stimulated with staphylococcal enterotoxin B and the ability of IFN- positive cells to co-produce TNF-, IL-2 and CD154 was evaluated as a measure of CD4 multi-function.

**Results**

Patients that did not mount a protective response to PCV-13 had a higher percentage of CD4+CD28null T-cells (median 16.7% IQR [10.2-20.2] vs. 3.2 [1.3-4.6]; p=0.001) and a higher percentage of directly measured CMV-specific CD4 T-cells (3.6 [1.6-9.8] vs. 0.4 [0.1-1.5]; p=0.004) compared to those that did. CD4+CD28null T-cell percentage and directly measured CMV-specific CD4 T-cell percentage were both negatively correlated with mean ARR (rho = -0.373, p=0.025 and rho = -0.437, p=0.008). In addition, patients with evidence of recent CMV reactivation had suppressed immune responses to PCV-13, compared to those with no reactivation (mean ARR 1.1 [1.0 – 1.6] vs. 3.6 [1.4 – 6.4], p=0.009). Increasing CD4+CD28null T-cell accumulation was associated with a decline in multi-functional (IFN-+TNF-+IL-2+CD154+) CD4 T-cells (rho = -0.663, p<0.001), whilst the relative proportion of multi-functional CD4 T-cells was positively correlated with the ARR to PCV-13 (rho = 0.345, p = 0.040).

**Conclusion**

The host immune response to CMV is associated with reduced CD4 function and diminished efficacy of a T-cell dependent pneumococcal vaccine. Prevention of asymptomatic reactivation of CMV in AAV may improve immune response to heterologous antigens and boost vaccine efficacy.