A Cytomegalovirus Vaccine for Transplantation: Are We Closer?

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(See the article by Wloch et al., on pages 1634–42.)

Cytomegalovirus (CMV), a betaherpesvirus, causes significant human morbidity and mortality. It is present in at least 60% of the US population [1], with a prevalence of >90% in high-risk groups, including men who have sex with men [2, 3]. In immunocompetent hosts, CMV infection is usually asymptomatic, but it persists throughout an individual’s lifetime and has the potential to reactivate and cause disease. CMV also causes significant disease in newborns, which can result in sensorineural hearing loss, other central nervous system abnormalities, and death. In immunocompromised individuals, CMV is the most common viral cause of severe disease, including gastrointestinal manifestations and pneumonia in the transplant population and, in addition, retinitis in HIV-positive individuals [4, 5].

Current management of CMV disease uses antivirals that may have significant hematopoietic and renal toxicities along with sometimes-adverse drug-drug interactions. Thus, an effective CMV vaccine would be beneficial in decreasing the need for anti-CMV drugs. In 2001, the Institute of Medicine reported that the development of a CMV vaccine is of the highest priority in the 21st century [6]. Vaccine strategies have targeted CMV structural proteins, including the major surface glycoprotein B (gB) and tegument phosphoprotein 65 (pp65), because they have been shown to induce the dominant antibody and cellular immune responses, respectively [7–9]. CMV nonstructural proteins that elicit a strong humoral response, such as immediate-early 1 (IE1), have also been used. Several CMV vaccines have been studied, with mixed results [10]. Initial animal studies have been performed using an alphavirus-like replicon particle that expresses various combinations of pp65, IE1, and gB, with promising results [11]. Studies with live attenuated human Towne strain CMV vaccine have been disappointing in that the vaccine has not prevented CMV infection in seronegative individuals [12–15]. A phase 1 study of live recombinant human CMV Towne/Toledo chimeric vaccines in CMV-seropositive subjects produced no significant cellular or humoral immune response to the vaccine [16]. A recombinant gB protein with MF59 adjuvant (gB/MF59) vaccine induced high levels of IgG antibodies to gB in healthy adults who were given 2 priming doses followed by a booster dose at 6 months [17]. A canarypox-CMV recombinant gB vaccine, ALVAC-CMV(gB), could not elicit a significant neutralizing antibody response [18], nor did it show benefit in a prime-boost strategy or in a simultaneous-vaccine strategy with the gB/MF59 vaccine [19].

Since immunocompromised individuals such as transplant recipients are a target population for CMV vaccination, it would be of benefit to use a virus-free vaccine [20]. DNA vaccines have been shown to induce significant T cell (both CD4+ and CD8+) and antibody responses [21] and, theoretically, for prolonged periods [22]. Alone, they are poorly immunogenic, but they can be combined with an adjuvant or modified to increase their immunogenic potential. They usually require large quantities of antigen to obtain a sufficient response, but they are relatively easy to produce.

In this issue of the Journal, Wloch et al. [23] present the results of a phase 1 clinical trial of a bivalent DNA CMV vaccine, VCL-CB01 [24], containing plasmids encoding for gB and pp65 along with poloxamer CRL1005 and benzalkonium chloride to increase immunogenicity. The trial was an open-label, dose-escalating study of 44 adults who were either seronegative or seropositive for CMV. Wloch et al. evaluated 2 doses, 1 and 5 mg, in a
3-dose schedule, with vaccine administered at weeks 0, 2, and 8. In addition, a group was evaluated using an accelerated 5-mg dose schedule, with vaccine administered on days 0, 3, 7, and 28. The primary objectives of the study were to assess the safety profile and immunogenicity of the vaccine.

The authors found VCL-CB01 to be well tolerated, with pain at the site of injection to be the most common adverse event (AE). Of the study participants, 81.8% developed a grade 1 AE, and 40.9% developed a grade 2 AE that resolved after several days. The AEs observed were not associated with dose or schedule. These results are comparable to those observed with other phase 1 trials of adult human CMV vaccines.

Immunogenicity was evaluated by assessing antibody and T cell responses to gB and pp65, respectively, at various time points up to week 32 after the initial vaccination. Using standard ELISA methods, a positive gB antibody response was defined as >2.5 times that of pooled CMV-seronegative serum specimens. In those individuals who developed antibody against gB, the measured serum anti-gB response was comparable to that observed in other CMV vaccine studies. Interestingly, no CMV-seropositive individual developed appreciable anti-gB antibody, and a small fraction of the CMV-seronegative individuals developed an anti-gB antibody response. Antibody levels peaked around weeks 12–16 after vaccination. It will be of interest to determine why CMV-seropositive individuals do not seem to mount a humoral response when reexposed to gB antigen and whether this response can be induced via additional vaccine doses or through a prime-boost strategy with other CMV vaccines.

T cell responses to VCL-CB01 were evaluated by pp65 ex vivo interferon (IFN)-γ enzyme-linked immunospot (ELISPOT) assays. They were considered to be positive if >50 sfu/1 × 10^6 peripheral blood mononuclear cells were present or there was a 2-fold increase in spot-forming units relative to that seen in controls. T cell responses were measured at several time points up to 16 weeks after vaccination. In CMV-seropositive individuals, 12.5%–37.5% had a T cell response to pp65, compared with 25.0%–50.0% of CMV-seronegative individuals; responses peaked at weeks 10–12 after vaccination. This response, too, is modest, faring better than the live recombinant CMV Towne/Toledo chimeric vaccine that failed to induce T cell responses [16] but not as well as the Towne CMV vaccine that showed a 45%–69% IFN-γ CD8+ T cell response with or without recombinant human interleukin-12 [25].

The highlight of Wloch et al.’s study is the use of the cultured IFN-γ ELISPOT assay to evaluate whether VCL-CB01 primed the T cell memory response at week 32, or 24 weeks after vaccination. The authors found a positive response to pp65 in 63.6% (14/22) and to gB in 59.1% (13/22) of CMV-seropositive participants, with 68.2% subjects (15/22) overall responding to either antigen. This strongly suggests that VCL-CB01 has the ability to prime T cells, such that, on rechallenge with antigen, antigen-specific T cells can proliferate and secrete IFN-γ. Moreover, a persistent response was observed when tested at weeks 16 and 32 in those subjects who received the 5-mg dose. In all, the VCL-CB01 vaccine at the 5-mg dose with a 3-dose schedule at weeks 0, 2, and 8 holds promise, because it elicits appropriate immunologic responses with typical AEs in CMV-seronegative individuals. Additional studies evaluating its effectiveness in preventing CMV infection and disease and the duration of immunity should be pursued. A limitation of current CMV vaccines studied to date, including VCL-CB01, have shown no to minimal immunologic responses in CMV-seropositive individuals. Further studies attempting to increase immunogenicity or identify other CMV antigens associated with disease in seropositive individuals would be beneficial.

References