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Cytomegalovirus –The Quest for an Effective Vaccine in Transplant Recipients Continues

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Cytomegalovirus (CMV) can cause congenital disease, lead to complications in immunocompromised patients, and may play a role in immunocompetent patients by complicating critical illness and accelerating immunosenescense. It has been deemed a high priority for vaccine development by the Institute of Medicine of the United States[1]. In patients with hematologic malignancy undergoing haematopoietic cell transplantation (HCT), CMV continues to be a cause of morbidity and mortality. Preemptive antiviral therapy based on CMV surveillance is widely used in transplant centres around the world but is hampered by drug toxicity, the need for at least weekly virologic and laboratory surveillance, breakthrough cases of CMV disease and indirect immunosuppressive effects of the virus[2]. Indeed, even today CMV seropositivity remains independently associated with overall mortality in HCT recipients[3]. Therefore, there has been an intensive search for alternative strategies that overcome these shortcomings. Strategies include new drugs with an improved adverse event profile that would allow prophylactic administration and immunotherapies aimed at correcting the immunologic defect caused by the HCT procedure[2]. One approach that has fascinated researchers since the inception of HCT is vaccination, which, in theory, would be safe, effective, and easy to administer. In the transplant setting, both therapeutic (i.e. vaccination of seropositive individuals) and preventive (vaccination of seronegative recipients) vaccination strategies have been studied. The option of vaccinating the HCT donor to induce or augment donor immunity before stem cell donation is a particularly intriguing concept since transfer of donor immunity has been shown to reduce infectious risk after transplantation, including that of CMV[4]. However, the obstacles to effective vaccination strategies early after allogeneic HCT are formidable due to the intense immunosuppression, poor vaccine responsiveness, and logistical problems with donor vaccination[5]. Indeed, until recently, vaccination of allogeneic HCT recipients was neither recommended nor attempted during the first 3-6 months after HCT[6]. Nevertheless,

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Conflict of Interest Statement

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progress has been made in recent years with early vaccination both for CMV and varicella zoster virus. Griffiths et al. showed in a phase II placebo controlled trial in solid organ transplant recipients that a glycoprotein B (gB) subunit vaccine with an adjuvant MF59 reduced CMV viremia by approximately 50%, most likely mediated by gB antibody responses[7]. Subsequently, in a phase II randomized placebo controlled trial Kharfan-Dabaja et al. demonstrated that a DNA vaccine that contained plasmids encoding the surface glycoprotein B and tegument phosphoprotein-65 with an adjuvant (CRL1005 poloxamer and benzalkonium chloride) reduced CMV reactivation and recurrence of reactivation by approximately 50% in seropositive allogeneic HCT recipients[5]. Donor vaccination that was originally part of the strategy in that study had to be abandoned due to lack of feasibility[5]. The vaccine increased CMV-specific T cell responses while antibody levels were not statistically significantly increased[5]. It is now undergoing phase III evaluation (www.clinicaltrials.gov NCT01877655). At the same time, several candidate vaccines are undergoing preclinical and clinical testing as recently reviewed by Plotkin[8].

In this issue of **The Lancet Haematology**, Nakamura et al. report results from a phase Ib placebo controlled trial of an adjuvanted peptide vaccine that was given to allogeneic HCT recipients[9]. The vaccine was safe and produced a CMV-specific CD8 T cell but no antibody response. Vaccine recipients had a reduced risk of CMV reactivation measured by PCR (relative hazard 0·12, 95% confidence interval 0·02-1·1), a shorter duration of anti-CMV antiviral drugs, and increased relapse-free survival (relative hazard 0·14, 95% confidence interval 0·01-0·94). The apparent effect on CMV viremia and relapse-free survival is remarkable but several caveats should be considered. First, due to the HLA restriction of the HLA A*0201 peptide only about one third of allograft recipients were eligible to participate. The authors also excluded patients receiving higher doses of corticosteroids, thereby excluding patients at the highest risk for CMV reactivation and complications of CMV; this exclusion criterion has been removed in the ongoing phase II trial (NCT02396134). Also, while the effects on CMV reactivation and relapse-free survival are impressive, the small sample size introduced significant uncertainty about the true magnitude of the vaccine effect as indicated by the wide confidence interval. These issues need to be considered when designing phase II and III studies.

What are the open questions towards the development of an effective CMV vaccine for immunocompromised patients and, ultimately, for the general population? One key question remains: what are the correlates of protective immunity in different clinical settings? It is still poorly understood why the risk of CMV differs between various immunocompromised hosts and what the immunologic correlates are that could explain these differences. While T cell immunity is believed to be important recent positive results with vaccines that stimulate neutralizing antibodies and the discovery of the pentameric complex require studies to determine the relative importance of T cells and antibodies for protective immunity[7, 10]. Experiences of a broad consortium that assessed dozens of diverse immune responses as correlates of vaccine efficacy in the RV144 Phase 3 HIV vaccine trial[11, 12] may suggest methodologic approaches to consider for CMV vaccine efficacy trials. The study design that stored baseline and postvaccination samples in all participants enabled the post-trial correlates study. A steering committee invited immunology labs at large to perform their

assays on RV144 pilot samples, and a centralized, independent statistical group conducted uniform data analysis to down-select assays with adequate signal-to-noise properties into the case-control correlates study. Immune response biomarkers derived from the selected assays were statistically optimized and partitioned into a primary analysis tier (hypothesis testing of several biomarkers covering hypothesized protective mechanisms) and an exploratory tier (hypothesis generation). A statistical analysis plan including correlates power calculations was finalized prior to unblinding that fully pre-specified the multivariable primary analysis for detecting significant correlates of outcome. Post primary analysis, investigators at large have been invited to submit concept proposals for additional statistical and assay analyses to generate additional hypotheses about correlates of vaccine efficacy.

Finally, the question of the overall goal of CMV vaccination in the immunocompromised patient must be raised. Is complete suppression of viral load achievable? More importantly, is it necessary or is suppression of direct and indirect CMV disease manifestations the ultimate goal in the context of a vaccine strategy? Given the paucity of clinical endpoints a viral load endpoint is clearly desirable. Moreover, a therapeutic vaccine might exercise benefit in the context of low-level reactivation by further boosting the immune response, however, more data is needed to confirm this hypothesis. The definition of a viral load threshold that correlates with clinical outcomes and optimizes vaccine responses constitutes a major unmet need.

Additional challenges towards a highly effective vaccination strategy that can be applied to the allogeneic HCT population at large are how to overcome the immunosuppressive effects of steroids and other drugs used to treat and prevent GVHD as well as T cell depletion, and how we can overcome feasibility issues to take advantage of donor vaccination.

Vaccinations of immunocompromised patients pose a particular challenge and correlates of protection may differ from those in immunocompetent individuals. The study by Nakamura et al. is important to the field and will hopefully energize researchers, industry and funding agencies to facilitate a broad-range research effort that will ultimately lead to CMV vaccines that are available for various populations at risk.

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References

1. Plotkin S, Sepe S, Myers M, Committee OBotSoFVNVA. Institute of Medicine Report: "Vaccines for the 21st Century" In: Services UDoHaH, editor. HHS.gov; 1999.
2. Boeckh M, Murphy WJ, Peggs KS. Recent advances in cytomegalovirus: an update on pharmacologic and cellular therapies. Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation 2015; 21(1): 24–9.
3. Ljungman P The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. Current Opinion in Hematology 2014; 21(6): 466–9. [PubMed: 25159712]

4. Zhou W, Longmate J, Lacey SF, et al. Impact of donor CMV status on viral infection and reconstitution of multifunction CMV-specific T cells in CMV-positive transplant recipients. Blood 2009; 113(25): 6465–76. [PubMed: 19369230]
5. Kharfan-Dabaja MA, Boeckh M, Wilck MB, et al. A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Infectious Diseases 2012; 12(4): 290–9. [PubMed: 22237175]
6. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2009; 15(10): 1143–238.
7. Griffiths PD, Stanton A, McCarrell E, et al. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. Lancet 2011; 377(9773): 1256–63. [PubMed: 21481708]
8. Plotkin S. The history of vaccination against cytomegalovirus. Medical Microbiology and Immunology 2015; 204(3): 247–54. [PubMed: 25791890]
9. Nakamura R, La Rosa C, Longmate J, et al. Cytomegalovirus chimeric epitope vaccine supplemented with PF03512676 (CMVPepVax) in allogeneic hematopoietic stem cell transplantation: improved viremia, immunogenicity and survival outcomes in a randomised phase 1b trial. The Lancet Haematology 2015; (In press).
10. Freed DC, Tang Q, Tang A, et al. Pentameric complex of viral glycoprotein H is the primary target for potent neutralization by a human cytomegalovirus vaccine. Proceedings of the National Academy of Sciences of the United States of America 2013; 110(51): E4997–5005. [PubMed: 24297878]
11. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med 2012; 366(14): 1275–86. [PubMed: 22475592]
12. Corey L, Gilbert PB, Tomaras GD, Haynes BF, Pantaleo G, Fauci AS. Immune correlates of vaccine protection against HIV-1 acquisition. Science Translational Medicine 2015; 7(310): 310rv7.