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Measuring Immune Response to Commonly Used Vaccinations in Adult Recipients of Allogeneic Hematopoietic Cell Transplantation

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Recipients of hematopoietic cell transplantation (HCT) are at risk for potentially preventable infectious complications because of defects in humoral and cell-mediated immunity. Studies of vaccine immunogenicity in HCT recipients have shown that antibody response rates depend on age, type of vaccine, and presence or absence of graft-versus-host disease. However, few large-scale studies have assessed the immune response to vaccination in HCT recipients. Additionally, HCT recipients have much higher rates of potentially preventable infections compared with the general population even after vaccination. This review evaluates the available studies and our view on the measurement of specific antibody titers, definition of an immune response, and durability of response in HCT recipients in both inactivated and live attenuated vaccines.

INTRODUCTION

Hematopoietic cell transplantation (HCT) recipients are at risk for infectious complications because of defects in humoral and cell-mediated immunity after transplantation. Recipients have decreased antibody titers against vaccine-preventable diseases if they are not revaccinated after HCT and are at increased risk of morbidity and mortality from vaccine-preventable diseases [1,2]. Vaccination guidelines have been published by 3 major societies, but it remains unclear how HCT patients should be monitored for vaccine response and durability.

Clinically significant response to immunization is defined as either a rise in antibody titer to a level that is accepted as protective or a 4-fold increase in antibody titer with at least partial recovery of B cell– and T cell–mediated immunity. Even HCT recipients who have had recovery of total B cell numbers may remain vulnerable to infection because of incomplete antigen-specific response by newly generated B cells [1,3,4]. B cell recovery is delayed in patients with chronic graft-versus-host disease (cGVHD), treatment with rituximab, and poor B cell engraftment [1,3]. Initial recovery of circulating T cell levels occurs primarily through expansion of mature T cell populations included in the graft with recovery delayed by older age and cGVHD [3]. Patients aged < 18 years without cGVHD may recover $CD4^+$ T cells > 200 cells/μL at 6 to 9 months post-HCT compared with >2 years for adults with cGVHD [3].

Studies of vaccine immunogenicity in HCT recipients have observed antibody responses at 3 to 12 months after transplant depending on age, type of vaccine, and presence or absence of GVHD [1]. Response to polysaccharide–protein conjugates is more robust than response to pure polysaccharide antigens [1,5,6]. Patients with cGVHD respond to vaccines, but both GVHD and its treatment impair antibody and T cell responses to vaccines [7,8]. The purpose of this review is to explore the evidence behind the immune response to vaccination in HCT recipients, including measurement of specific antibody titers, definition of an immune response, and durability of response.

PNEUMOCOCCAL

Invasive pneumococcal disease is 1 of the most common causes of vaccine-preventable morbidity and mortality in HCT recipients. Multicenter studies have reported the incidence of invasive pneumococcal disease between 9 and 22.5 per 1000 recipients of allogeneic HCT and between 3.8 and 6.2

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per 1000 recipients of autologous HCT, with most 14 to 28 months post-transplant [1,7-9].

Two vaccines against *Streptococcus pneumoniae* are available: PPSV23, a polysaccharide capsular vaccine, and PCV13, a protein-conjugated vaccine. Conjugated pneumococcal vaccines generate a T cell–dependent immune response that triggers a memory B cell response, conferring a more robust and durable immune response than PPSV23. PPSV23 was originally recommended in the first year after HCT, but there is limited efficacy because of the time required to regenerate T and B cell responses. Studies then showed that PCV7, a 7-valent pneumococcal conjugate vaccine, demonstrated favorable immune responses, so recommendations included PCV7 [10-13]. After the introduction of PCV13, current recommendations have shifted to the use of PCV13 because it improves immunogenicity [14,15].

Challenges to the interpretation of studies of the immunogenicity of pneumococcal vaccination include the definition of protective antibody response and the presence of multiple pneumococcal serotypes. Based on large studies of PCV7 efficacy and immunogenicity in healthy infants and children, a World Health Organization working group defined a pooled efficacy estimate of 93% with a pooled protective antibody titer of ≥.35 μg/mL [16,17] but there is no defined protective threshold value in adults [18-20]. Additionally, there was concern that IgG titers may not be functional in HCT recipients because of impaired opsonophagocytosis. Thus, opsonophagocytic assays have been developed to measure opsonization of pneumococci by serum samples in vitro that correlated well with IgG titers, indicating that IgG titers are an appropriate surrogate for the immune response [21].

The studies reviewed above have shown that pneumococcal vaccination generates functional antibodies against *S. pneumoniae*, but few studies have examined the durability of the immune response. Cordonnier et al. assessed persistence of immune response 10 years after vaccination in a subgroup of 30 surviving participants in the European Group for Blood and Marrow Transplantation Infectious Diseases Working Party 1 (IDWP01) [14,15]. Persistent response rate to all 7 serotypes was found to be 65.5% for antibody cut-off .15 μg/mL and 40% for antibody cut-off .5 μg/mL, which is similar to those observed at 24 months after vaccination. The only factor found to affect persistence of response was timing of initial vaccination. As shown originally in the IDWP01 trial, patients who received 3 doses of PCV7 beginning at 3 months after transplant followed by a PPSV23 booster at 12 months had lower antibody levels at 24 months compared with patients who received the PCV7 series beginning at 9 months with PPSV23 booster at 18 months [15]. This difference in response was postulated to be due to more advanced immune recovery at 9 months after HCT.

With the introduction of PCV13, a study by Cordonnier et al. [14] hypothesized that 4 doses of PCV13 administered after HCT may generate a more robust immune response than 3 doses. In their study, 251 adult and pediatric allogeneic HCT recipients received 3 doses of PCV13 at 1-month intervals, a fourth dose of PCV13 6 months later, and 1 dose of PPSV23 1 month later. Geometric mean fold rises of IgG geometric mean concentrations (GMCs) increased significantly for all pneumococcal serotypes from baseline to postdose 3, decreased significantly postdose 3 to predose 4, and increased significantly postdose 4. GMCs were similar pre- and post-PPSV23, but both adult and total study populations had significantly higher GMCs against serotype 9V after PPSV23. Pediatric and total populations had significantly lower GMCs against 6B, with all groups having significantly lower GMCs against serotype 6A (not included in PPSV23). There was a correlation between response measured by IgG titers and opsonophagocytic assays [22,23]. These results suggest that 3 doses of PCV13 followed by a fourth booster dose is likely more immunogenic than 3 doses of PCV13 alone. The authors observed increased rates of local site reactions after the fourth dose of PCV13 (13/192 adult patients) but found the overall safety profile acceptable. The purpose of administering PPSV23 is to extend serotype coverage, but this study did not evaluate response to the 11 serotypes unique to PPSV23. Further studies are needed to characterize the role of PPSV23 in broadening antipneumococcal coverage.

Current guidelines recommend administration of 3 doses of PCV13, beginning at 6 months after transplant, with a booster dose of PPSV23 at 12 months for patients without cGVHD or a fourth dose of PCV13 at 12 months for patients with cGVHD [17]. It is currently not possible to give clear recommendations regarding protective antibody titers because of a lack of standardized testing and the many different serotypes of pneumococci.

INFLUENZA

Influenza infection incidence varies by year and geographic location but can be associated with significant morbidity and mortality rates up to 30% in untreated HCT patients [1,3,4,24]. Two categories of influenza vaccine are available: inactive influenza vaccine (IIV), which does not contain any replicating virus, and live attenuated influenza vaccine, which contains strains that replicate in nasopharyngeal epithelial cells [4,25-27]. Only IIV is recommended for use in HCT recipients, as no data are available regarding the safety and efficacy of live attenuated influenza vaccines in the setting of HCT [28].

A challenge to the measurement of serologic response to influenza immunization is that the vaccine strains included may change depending on those expected to circulate in the population during the next season, which is based on antigen drift and possibly shift in circulating influenza strains [4]. A 2013 meta-analysis, which included 10 randomized controlled trials performed in healthy adults ages 18 to 65, found a pooled efficacy of 59% against reverse transcriptase PCR or viral culture–confirmed influenza in 8 of 12 seasons analyzed [28]. Significant variability was found, however, depending on season and age group.

Unfortunately, most studies have demonstrated poor seroconversion rates in the HCT population. Gandhi et al. found low rates of seroconversion after immunization with IIV at 11 months after autologous peripheral blood stem cell transplantation or bone marrow transplantation (BMT), with no serologic response in allogeneic HCT recipients [29]. A study by Pauksen et al. of 117 recipients of autologous and allogeneic HCT found similarly low response rates [30]. However, Engelhard et al. found that increasing time after transplant was positively correlated with development of protective antibody titer with no response <6 months after HCT [31]. The studies referenced above defined hemagglutinin titers ≥ 1:40 as protective with serologic response defined as at least a 4-fold rise in hemagglutinin titers [31].

During the 2009 H_1N_1 pandemic, further serologic studies were done. Engelhard et al. evaluated response to 1 and 2 doses of commercial adjuvanted vaccine in 78 adult and pediatric recipients of allogeneic and autologous HCT [32]; 17.9% of patients had HA titer ≥ 1:40 at baseline compared with 44.2% of patients after 1 dose and 48.8% of patients after 2