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Safety of High Dose Trivalent Inactivated Influenza Vaccine in Pediatric Patients with Acute Lymphoblastic Leukemia

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Background. Although children with acute lymphoblastic leukemia (ALL) mount immune responses after vaccination with the trivalent influenza vaccine (TIV), these responses are lower compared to controls. Recently, a high dose (HD) TIV was found to increase the level of antibody response in elderly patients compared to the standard dose (SD) TIV. We hypothesized that the HD TIV would be well-tolerated and more immunogenic compared to the SD TIV in pediatric subjects with ALL. ***Procedure.*** This was a randomized, double-blind, phase I safety trial comparing the HD to the SD TIV in children with ALL. Our secondary objective was immunogenicity. Subjects were randomized 2:1 to receive either the HD (60 μg) or the SD (15 μg) TIV. Local and systemic reactions were solicited, hemagglutinin inhibition titers to influenza virus antigens were measured, and monitoring labs were collected prior to and/or after each vaccination. ***Results.*** Fifty subjects were enrolled (34 HD, 16 SD). Mean age was 8.5 years; 63% were male, and 80% were in maintenance therapy. There were no significant differences reported in local or systemic symptoms. No severe adverse events were attributed to vaccination. No significant differences between the HD and SD TIV groups were noted for immune responses. ***Conclusions.*** No differences were noted between the HD and SD TIV groups for solicited systemic and local reactions. Since this study was not powered for immunogenicity, a phase II trial is needed to determine the immunogenicity of HD versus SD TIV in the pediatric ALL population. Pediatr Blood Cancer 2014;61:815–820.

Key words: children; influenza; leukemia; trivalent inactivated influenza vaccine

INTRODUCTION

Influenza is an important cause of morbidity and mortality worldwide. Influenza A and/or B viruses cause yearly epidemics in the United States, with an average of 36,000 deaths and 114,000 hospitalizations each year [1]. Children have the highest rates of infection, whereas elderly adults have the highest mortality rates [2,3]. However, half of the deaths occur in other groups with risk factors [2,3]. These risk groups include immunocompromised individuals, particularly those with acute lymphoblastic leukemia (ALL). ALL patients experience immune suppression both from their disease and secondary to chemotherapy, which they receive for up to 3.5 years [2,3]. Children with cancer also have a higher frequency of influenza infections and longer duration of symptoms compared to healthy individuals. Furthermore, they are more likely to be hospitalized due to influenza illness.

A recent study by Tasian et al. [4] reported results from a 5-year retrospective review of pediatric children with cancer who had proven influenza A or B infection from July 1, 2000 to June 30, 2005. The investigators identified 27 clinical encounters in 24 oncology patients (63% with hematologic cancer), with two-thirds of the patients hospitalized for a median duration of 7.4 days, and 40% of them experienced a delay in chemotherapy as result of influenza infection [4]. In addition, 15% of the subjects had concurrently diagnosed bacteremia. Others have reported severe and fatal complications due to influenza disease in this population, such as secondary bacterial infections and hemophagocytic syndromes [5–8], including serious complications from the 2009 pandemic influenza A H1N1 [9]. In addition, immunosuppressed individuals can shed influenza virus for prolonged periods when infected, resulting in nosocomial outbreaks and development of resistant strains [10–12].

The main protection from influenza disease is influenza vaccination. Therefore, yearly influenza vaccination is recommended for high-risk individuals, including patients with ALL [13]. Contemporary influenza trials with the trivalent inactivated influenza vaccines (TIVs) demonstrated that children with ALL mount an immune response; [14–19] however, these studies also confirmed lower titers and seroresponse rates to influenza vaccines in children with ALL compared to healthy controls. In addition, lower titers were observed in those who received chemotherapy compared to those off chemotherapy [14,15,19].

A high dose (HD) TIV (Fluzone HD) with four times the antigenic dose was approved in individuals ≥65 years of age, because this population was historically noted to respond poorly to the standard dose (SD) TIV compared to younger adults [20]. A phase III study found a statistically significant higher antibody response to both influenza A antigens in elderly patients who received the HD vaccine compared to those who received the SD

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TIV, thus leading to its licensure. Accordingly, since children with ALL have a lower response rates to the TIV compared to healthy controls, administering a HD TIV in this population could improve their immune response to influenza vaccines. Therefore, we sought to determine the safety of HD TIV compared to SD TIV in children with ALL.

METHODS

Study Design

This was a prospective, randomized, double-blind, 2:1, phase I safety study comparing the HD TIV to the SD TIV in pediatric subjects with ALL who were 3–17 years of age (Clin-Trials.gov: NCT01216332). Our secondary objective was immunogenicity. Subjects were randomized in a 2:1 fashion to receive 0.5 ml of either the HD or SD TIV intramuscularly. Subjects less than 9 years of age received either one or two doses of the vaccine based on ACIP recommendations. The study was approved by the Vanderbilt University Institutional Review Board and conducted in the outpatient oncology clinic at Vanderbilt Children's Hospital during the 2010–2011 and 2011–2012 influenza seasons.

Subjects

Pediatric subjects who were between the ages of 3 and 17 years with standard or high risk ALL, who were available for the entire study period and whose parents or guardians provided consent were eligible to participate. These subjects must have been in a first complete remission and at least 4 weeks into maintenance therapy in study year 1 and at least 4 weeks into chemotherapy in study year 2. Inclusion criteria were broadened in study year 2 in attempts to increase enrollment numbers because safety data were not thought to be significantly affected by phase of chemotherapy. Subjects were screened and recruited from the oncology clinic at Vanderbilt Children's Hospital. Subjects were excluded if they (1) had a history of hypersensitivity to previous influenza vaccination or to eggs/egg protein; (2) had a history of Guillain–Barre syndrome; (3) had evidence of relapsed disease; (4) had a history of receiving the current season's (2010–2011 or 2011–2012) influenza vaccine or had proven influenza disease during the current season; (5) were a pregnant female; (6) had a hematopoietic stem cell transplant; (7) had a platelet count of less than 50,000 cells/μl; (8) had a history of known infection with HIV, hepatitis B or hepatitis C; (9) had a history of known latex hypersensitivity; or (10) had any condition that would, in the opinion of the site investigator, place them at an unacceptable risk of injury, render them unable to meet the requirements of the protocol or interfere with successful completion of the study. In addition, the criteria for temporarily delaying vaccine administration included: a fever ($\geq$100.4˚F/38.0˚C) or acute illness within 48 hours of enrollment, or receipt of any live vaccines within 4 weeks or any inactivated vaccines within 2 weeks of study vaccination.

Vaccine

All subjects received either the SD TIV (Fluzone, Sanofi Pasteur) or HD TIV (High Dose Fluzone, Sanofi Pasteur). The 2010–2011 and 2011–2012 influenza vaccines were used for their respective influenza seasons, which contained 0.5 ml of either 15 or 60 μg, respectively, of each of the following: A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus. Subjects were recommended to receive the vaccination intramuscularly in the right or left deltoid and were then observed closely for at least 20 minutes post-vaccination. If subjects required two doses of the TIV, the doses were separated from each other by 28 (+7) days.

Primary Objective: Safety Evaluation

Parents or guardians were asked to record solicited reactogenicity events, which included: local reactions (pain, tenderness, redness, swelling, and induration at the injection site) and systemic reactions (fevers, fatigue/malaise, headache, nausea, body ache/myalgia, general activity level, and vomiting), for 7 days following vaccination. Local and systemic reactions were graded on a scale from 0 to 3 (Supplemental Tables I and II). The subjects were asked to report systemic symptoms that were different from baseline symptoms associated with chemotherapy. Study personnel contacted the subjects by telephone between 1 and 3 days and at 8 and 10 days after vaccination to review any adverse events (AEs) and serious adverse events (SAEs). AEs were collected for 28 days after last vaccination, and SAEs were collected through 180 days after their final vaccination via phone call and medical chart review.

Secondary Objective: Immunogenicity Evaluation

Serum samples were obtained by central lines on all subjects before administration of the first dose of the TIV and 28 (+7) days after final administration of the TIV. In study year 2, subjects who required two doses had serum samples obtained prior to administration of the first dose and 28 (+7) days after the first and second vaccine doses. Clinical labs were sent to the local laboratory at Vanderbilt University for a complete blood count, serum quantitative immunoglobulin (IgG) levels and quantitative CD4, CD8 and CD19 before administration of the vaccine, and 28 (+7) days after the final vaccination. Sera were centrifuged and frozen until shipment to a central laboratory (investigator JAM) in Memphis, TN for hemagglutination inhibition (HAI) testing.

HAI Testing

Sera were stored at −20˚C until the time of HAI analysis. The primary response was the detection of influenza-specific antibodies for the three influenza strains included in the vaccine (A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008) as measured by HAI, as previously described [21]. For determination of HAI titers, individual virus stocks expressing hemagglutinin from A/California/7/09 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 were adjusted to four hemagglutinin units and incubated with diluted sera for 1 hour at 4˚C. Chicken red blood cells (0.5%) were added to the plates, and HAI titers, reported as the reciprocal of the final serum dilution that inhibits hemagglutination, were recorded 30 minutes later. Assays were repeated at least once and up to thrice to assure concordance of the final reported titer. Results were expressed as geometric mean titers (GMTs) with 95% confidence intervals; seroprotection rates, defined as the percentage of subjects achieving an HAI titer $\geq$1:40; and seroconversion rates, defined as the percentage of subjects achieving at least a fourfold increase in HAI titers from a seropositive pre-vaccination titer ($\geq$10) or a rise from $<$10 to $\geq$40

in those who were seronegative. A value of 5 was used for determination of GMTs when the titer was <10.

Statistical Analysis

Descriptive statistics were calculated as the median with interquartile range (IQR) or percentages (frequencies) as appropriate. The HD group was compared to the SD group using the Wilcoxon rank sum test or Pearson's Chi-square test. GMTs from each study visit were presented with 95% bootstrap confidence interval. We used logistic regression models to assess the treatment effect on the seroconversion and seroprotection with adjustment for IgG and CD19 levels. All tests were two-tailed, with a significance level of 0.05. Statistical analyses were performed using open source R statistical software (version 2.15.1, Vienna, Austria).

RESULTS

Subjects

During the two influenza study seasons, of the 66 subjects approached, 50 subjects were enrolled (20 in year 1 and 30 in year 2), with 16 in the SD group and 34 in the HD group. Nine subjects in the HD TIV group and two subjects in the SD TIV group required two doses of the vaccine. Four subjects were excluded from the data analysis, because they were given the second dose of TIV outside the study window period. The mean, median, and IQR of ages for children from the HD TIV group were 8.3, 7.2, and 4.8–11.4 years, respectively. The mean, median, and IQR of ages for children from the SD TIV group were 8.9, 8.7, and 5.8–11.4 years, respectively. Eighty percent of all patients were enrolled during the maintenance phase of chemotherapy. Demographics and clinical characteristics comparing the SD TIV group to the HD TIV group are found in Table I. The two groups were comparable except for the CD19 counts, which were lower in the HD group (median of 9.0) compared to the SD group (median of 25, $P = 0.025$).

Primary Objective: Safety Data

The majority of local and systemic reactions for both vaccine groups in the 7 days after vaccination were grades 1 or 2 and most of these reactions occurred in the first few days (days 0–2). A summary of reactogenicity events following vaccination is reported in Figure 1. Although the SD group reported more frequent reactogenicity events combined compared to the HD TIV group, this did not reach statistical significance. This was consistent for subjects receiving either one or two doses of the vaccine (SD TIV, one dose: 94% and two doses: 100% vs. HD TIV, one dose: 70% and two doses: 60%, $P = 0.063$ and 0.29, respectively).

The most commonly reported local reactions reported for both SD and HD TIV groups were pain (43% and 40%) and tenderness (56% and 47%). The most common systemic reactions reported were fatigue (56% and 30%) and decrease in general activity level (44% and 33%), respectively. There were a total of nine SAEs reported in the HD group and seven SAEs reported in the SD group. No SAEs were related to vaccination.

Secondary Objective: Immunogenicity Data

Complete immunogenicity data were available for all three influenza strains in 44 of 50 subjects. In addition to the four subjects mentioned earlier who were excluded, two additional subjects were excluded due to lack of complete immunogenicity data. Complete immunogenicity results are reported in Table II (% with ≥1:40 titers

TABLE I. Demographics and Clinical Characteristics of Subjects Receiving Either High Dose or Standard Dose Influenza Vaccine

Characteristic	N	All subjects (n = 46)	HD vaccine (n = 30)	SD vaccine (n = 16)	*P*-value
Median age, years (IQR)	46	8.0 (5.0–11.4)	7.2 (4.8–11.4)	8.7 (5.8–11.4)	0.68[a]
Gender (male), n (%)	46	29 (63%)	18 (60%)	11 (69%)	0.56[b]
Race, n (%)	46				0.8[b]
White, non-Hispanic		41 (89%)	27 (90%)	14 (88%)	
Black		5 (11%)	3 (10%)	2 (12%)	
Ethnicity	46				0.079[b]
Hispanic		6 (13%)	2 (7%)	4 (25%)	
Non-Hispanic		40 (87%)	28 (93%)	12 (75%)	
Chemotherapy Phase, n (%)	46				0.46[b]
Consolidation		3 (7%)	1 (3%)	2 (13%)	
Interim maintenance		4 (9%)	3 (10%)	1 (6%)	
Delayed intensification		2 (4%)	2 (7%)	0 (0%)	
Maintenance		37 (80%)	24 (80%)	13 (81%)	
WBC count, median (IQR)	46	3.0 (2.2–4.0)	3.1 (2.2–3.9)	3.0 (2.4–4.5)	0.78[a]
Hemoglobin, median (IQR)	46	11.4 (10.3–12.9)	11.5 (11.0–12.4)	11.1(10.2–13.1)	1[a]
Platelet count, median (IQR)	46	250 (201–305)	253 (205–341)	222 (173–270)	0.21[a]
IgG, median (IQR)	46	556 (379–706)	491 (358–657)	600 (559–720)	0.07[a]
CD4, median (IQR)	43	304 (220–388)	301 (196–394)	304 (254–370)	0.71[a]
CD8, median (IQR)	43	258 (156–372)	251 (132–337)	277 (234–534)	0.14[a]
CD19, median (IQR)	43	10.0 (4.5–42)	9.0 (3.8–17.2)	25 (10–66.5)	0.025[a]
ANC, median (IQR)	46	1,878 (1,072–2,701)	2,000 (1,062–2,629)	1,454 (1,082–2,780)	0.79[a]
ALC, median (IQR)	46	661 (414–1,002)	602 (381–976)	672 (599–1,173)	0.15[a]
Prior influenza vaccination, n (%)	46	42 (91%)	28 (93%)	14 (88%)	0.5[b]
Patients requiring two doses	46	7 (15%)	5 (17%)	2 (13%)	1[b]

n, number of subjects; HD, high dose; SD, standard dose; IQR, interquartile range; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count. Tests used: [a]Wilcoxon test, [b]Pearson test.

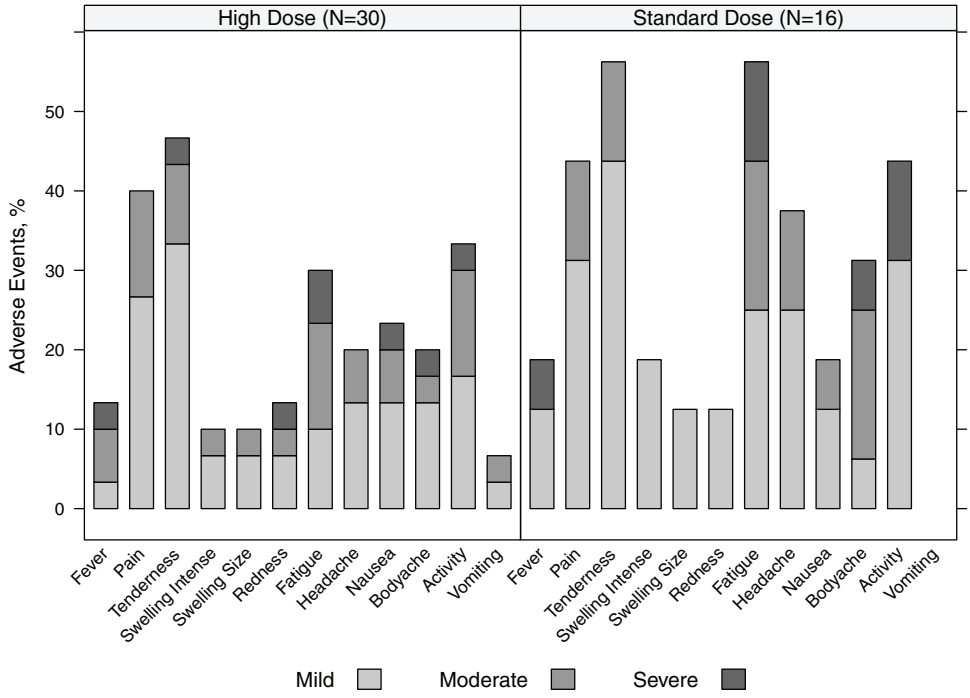

Fig. 1. Summary of reactogenicity events following vaccination.

before and after vaccination, % who achieved a fourfold increase or greater, and GMTs before and after vaccination). Pre-vaccination and post-vaccination GMTs were similar in the HD and SD TIV groups for all three strains (A/California/7/09/H1N1, A/Perth/16/2009/H3N2, B/Brisbane/60/2008), regardless of whether they received one or two doses of vaccine.

The majority of subjects required only one dose of TIV. Of the 24 subjects who received one dose of HD TIV and 13 who received SD, the majority of subjects achieved ≥1:40 titers (Table II). On the other hand, the majority of subjects did not achieve a fourfold rise in titers in both groups, especially for B and H3N2. Of note, over two-thirds of subjects had pre-titers ≥1:40 for H1N1 and B.

The five subjects in the HD group who received two doses of TIV, 80% of subjects achieved ≥1:40 titers for all three influenza strains. The percentage of subjects that achieved a ≥fourfold rise in titers for H1N1, H3N2, and B respectively was 80%, 60%, and 40%. Two subjects in the SD group required two doses of TIV; both subjects achieved ≥1:40 titers and ≥fourfold rise in titers for the H1N1 strain, only one subject achieved ≥1:40 titers and ≥fourfold rise in titers for H3N2, and both subjects achieved ≥1:40 titers but only one had a ≥fourfold rise in titers for the B strain.

TABLE II. Immunogenicity Results in High Dose and Standard Dose Vaccine Subjects, for those Who Required One Dose of Vaccine

		HAI		
Antigen	Titers, % (n/N)	All subjects (N = 37)	SD (N = 13)	HD (N = 24)
A/California/7/09 H1N1	≥Fourfold rise	32% (12/37)	46% (6/13)	25% (6/24)
	Pre-titer ≥1:40	70% (26/37)	69% (9/13)	71% (17/24)
	Post-titer ≥1:40	84% (31/37))	85% (11/13)	83% (20/24)
	GMT pre-vaccine	57.4 (36.4–92.0)	87.4 (37.9–209.1)	46.2 (27.4–75.7)
	GMT post-vaccine	148.9 (91.2–248.6)	322.9 (141.3–792.1)	97.9 (61.1–166.3)
A/Perth/16/2009 H3N2	≥Fourfold rise	35% (13/37)	38% (5/13)	33% (8/24)
	Pre-titer ≥1:40	43% (16/37)	54% (7/13)	38% (9/24)
	Post-titer ≥1:40	57% (21/37)	62% (8/13)	54% (13/24)
	GMT pre-vaccine	28.5 (20.5–39.5)	28.8 (18.1–46.5)	28.3 (18.7–43.3)
	GMT post-vaccine	67.4 (41.7–110.0)	76.5 (36–176.5)	62.9 (34.6–122.2)
B/Brisbane/60/2008	≥Fourfold rise	5.4% (2/37)	0% (0/13)	8.3% (2/24)
	Pre-titer ≥1:40	86% (32/37)	85% (11/13)	88% (21/24)
	Post-titer ≥1:40	76% (28/37)	69% (9/13)	79% (19/24)
	GMT pre-vaccine	62.7 (52.6–74.4)	56.1 (43.9–69.4)	66.5 (51.8–82.2)
	GMT post-vaccine	65.0 (48.5–87.9)	50.6 (35.3–67.3)	74.4 (49.9–111.6)

HAI, hemagglutination inhibition assay; HD, high dose; SD, standard dose; GMT, geometric mean titer.

A regression analysis was performed looking at the association between the rates of seroprotection and seroconversion comparing SD or HD TIV, with adjustments for the IgG and CD19 levels from the first visit. No differences were noted in seroprotection or seroconversion after adjustments for IgG and CD19 levels. A Pearson test was performed to analyze the effect of previous TIV vaccination on response to the current TIV and no significant differences in seroprotection or seroconversion for any of the influenza strains were noted.

DISCUSSION

Our phase I safety study demonstrated that the HD TIV was well tolerated compared to the SD TIV in this high risk population, with no major serious AEs associated with influenza vaccination. We found that solicited local and systemic events were comparable for both SD and HD recipients. Subjects who received the SD TIV were more likely to report any systemic or local reaction compared to the HD group; however, this did not reach statistical significance.

The majority of subjects reported at least one solicited event. For both vaccine groups, pain and tenderness were the most common local reactions reported and fatigue and decrease in general activity level were the most common systemic reaction. Most importantly, the majority of symptoms reported in either group were mild and resolved quickly. Few SAEs were reported and none of these were attributed to the vaccine. Our results differ from the three previous studies with the elderly population in which they reported higher rates of local reactions in HD TIV recipients compared to SD TIV recipients; however, these reactions were also well tolerated in the elderly [14,23–25].

Although this study was not powered to compare the immunogenicity between vaccine groups, the GMTs and the percentage of subjects achieving a $\geq$1:40 or fourfold rise in titers were not statistically different between those in the HD TIV or SD TIV groups. Our analyses separated the group comparisons further by those who received one or two doses of the vaccine, further limiting the sample size. We additionally analyzed the immunogenicity results by comparing the two study years and found no significant differences. Since this study was not powered for immunogenicity, a phase II trial is needed to determine the immunogenicity of HD versus SD TIV in the pediatric ALL. In addition, pre-titers in both groups were high, especially with H1N1 and B, which could have been due to prior vaccination or prior infection; these results may have further limited our ability to evaluate vaccine responses.

Even though we did not actively monitor for influenza illness, two subjects in year 1 of the study were hospitalized for influenza B and both subjects received the SD TIV. Four months after receiving the SD TIV, one of the subjects was hospitalized for 3 days. Five months later after receiving the SD TIV, a second subject was hospitalized for a total of 6 days. In addition to influenza B, coronavirus was detected in this subject. Both subjects received treatment with oseltamivir and recovered from their illnesses. We do not know if the influenza B virus that was detected in these patients represented the same vaccine strain of influenza B, since reports of two different influenza B strains simultaneously circulating have been reported.

Studies published in the 1970s and 1980s investigated influenza vaccine immune responses in patients with ALL and provided conflicting reports [23–33]. These discrepancies may be explained by the use of different influenza vaccines: monovalent, bivalent, or trivalent; whole cell versus split cell; and varying doses (from 50 to 400 chicken cell-agglutinating); different immunization schedules; different chemotherapeutic regimens; and most importantly inadequate samples sizes in those that did not find a statistically significant difference between children with and without cancer [23]. The majority of these earlier studies; however, reported that lower antibody titers were achieved in individuals with cancer, including children with ALL, when compared to healthy controls [23]. In addition, individuals receiving chemotherapy had significantly lower titers compared to those off chemotherapy [23]. Lower immune responses in children with ALL receiving chemotherapy compared to healthy controls and children with ALL off-chemotherapy were also reported in more current studies with TIV [14,15,19]. Two studies compared TIV to a live-attenuated influenza vaccine (LAIV) in children with cancer; the first study proved it was safe to administer LAIV in these children [22]. However, the second study revealed that the LAIV produced lower HAI titers compared to the TIV [21], suggesting that the LAIV was not as effective in this population compared to the TIV. Thus, these studies indicated that the optimal influenza vaccine does not exist at this time, and therefore this population could benefit from further research into improved influenza vaccines.

Our study has several limitations. This was a phase I study with a small number of patients enrolled and although we did not see any increased local or systemic reactions associated with the HD TIV, further studies with a larger population are needed. Recruitment occurred over two influenza seasons which is not ideal, but the vaccine formulations remained identical. Even though we limited our patients to children with ALL in remission and at least 4 weeks into the initiation of chemotherapy, this was still a heterogeneous population, which could have affected our immunogenicity results. Finally, we changed our inclusion criteria in study year 2, which allowed patients to enroll after 4 weeks into chemotherapy rather than once in the maintenance phase. Patients enrolled prior to the maintenance phase of chemotherapy are receiving more intense therapy and this might have affected their immune response to the vaccine in study year 2. Since more than 80% of patients were in maintenance during the study, the population was quite similar.

In conclusion, our study revealed that the HD TIV is safe and well-tolerated in children with ALL compared to SD TIV. A phase II trial is required to assess the immunogenicity of the HD TIV in patients with ALL. More importantly, since influenza viruses continue to cause high morbidity and mortality, and children with ALL do not respond adequately to SD TIV, finding a better influenza vaccine for this population could be of great benefit.

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