Low seroconversion after one dose of AS03-adjuvanted H1N1 pandemic influenza vaccine in solid-organ transplant recipients

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BACKGROUND: Immunocompromised individuals are more susceptible to complications produced by influenza infection. As a result, solid-organ transplant (SOT) recipients were targeted as a priority group to receive AS03-adjuvanted H1N1 influenza vaccine during 2009.
OBJECTIVE: To evaluate seroconversion after one dose of adjuvanted pandemic influenza H1N1 (pH1N1) vaccine in SOT recipients.
METHODS: Adult SOT recipients were enrolled to receive one 3.75 µg dose of adjuvanted pH1N1 vaccine. Serological status was tested using a hemagglutination inhibition assay before and two and four weeks postvaccination.
RESULTS: The five SOT recipients (one liver, two kidney and two lung transplants) had a median age of 50 years (range 36 to 53 years), and three were male, who were a median time of three years (range two months to 15 years) post-transplant. All patients were on a double or triple immunosuppressive regimen. The prevaccination pH1N1 titre was 1:10 in four patients and 1:40 in one patient. Seroprotection was observed only in one patient, with a rise in titre from 1:40 at baseline to 1:320 at both two and four weeks after vaccination. This lung transplant recipient had documented previous infection with pH1N1.
CONCLUSION: Results of the present small study call into question whether one dose of adjuvanted pH1N1 vaccine can provide seroprotection in SOT recipients.

Key Words: *H1N1; Immunogenicity; Influenza; Solid organ; Transplant; Vaccine*

Une séroconversion peu élevée après une dose du vaccin contre la grippe pandémique H1N1 contenant l'adjuvant AS03 chez des receveurs d'une transplantation d'organe plein

HISTORIQUE : Les personnes immunocompromises sont plus vulnérables aux complications de l'infection par l'influenza. Par conséquent, les receveurs d'une transplantation d'organe plein (TOP) faisaient partie des groupes prioritaires appelés à recevoir le vaccin contre la grippe pandémique H1N1 contenant l'adjuvant AS03 en 2009.
OBJECTIF : Évaluer la séroconversion après une dose du vaccin contre la grippe pandémique H1N1 contenant l'adjuvant (pH1N1) chez les receveurs d'une TOP.
MÉTHODOLOGIE : Les receveurs d'une TOP d'âge adulte ont été retenus afin de recevoir une dose de 3,75 µg du vaccin pH1N1 contenant l'adjuvant. Les chercheurs ont vérifié leur statut sérologique au moyen de la réaction d'inhibition de l'hémagglutination avant la vaccination, puis deux et quatre semaines plus tard.
RÉSULTATS : Les cinq receveurs d'une TOP (un foie, deux reins et deux poumons) avaient un âge médian de 50 ans (plage de 36 à 53 ans), trois étaient de sexe masculin et avaient subi leur transplantation depuis une médiane de trois ans (plage de deux mois à 15 ans). Tous les patients étaient sous bithérapie ou trithérapie immunosuppressive. Le titrage du pH1N1 avant la vaccination était de 1:10 chez quatre patients et de 1:40 chez un patient. Les chercheurs ont observé une séroprotection chez seulement un patient, son titre étant passé de 1:40 avant le vaccin à 1:320 tant deux que quatre semaines après la vaccination. Ce receveur d'une transplantation de poumon avait eu une infection par la pH1N1 attestée.
CONCLUSION : Les résultats de la présente petite étude mettaient en doute la capacité d'une dose du vaccin pH1N1 contenant l'adjuvant à assurer une séroprotection chez les receveurs d'une TOP.

Solid organ transplant (SOT) recipients are more susceptible to complications related to influenza and may experience prolonged viral shedding (1,2). As a result, it was believed that they would also be more susceptible to pandemic influenza H1N1 (pH1N1) than the general population (3-5). Therefore, SOT recipients were targeted as a priority for pH1N1 vaccination (6).

However, few studies have assessed the immunogenicity of the adjuvanted pH1N1 vaccine in this group. Studies measuring the immunogenicity of a single dose of pH1N1 vaccine in the general population have reported seroconversion rates >95% (7). Seroconversion is known to be lower in patients with cancer and pediatric heart transplant recipients (8-10). In pediatric liver transplant patients, the seroprotection rate was 53.8% (11).

The AS03-adjuvanted pH1N1 vaccine (8) was used in 2009 to control the epidemic situation that arose, although no robust clinical trials with the adjuvanted vaccine involving SOT recipients had been performed previously. Furthermore, although a single dose of this vaccine was advocated for use in Canada (12), it was unknown whether one dose of this preparation was adequate for immunocompromised patients because others have used two doses (13). Given the lack of data in this group of patients, we evaluated the seroconversion after one dose of adjuvanted pH1N1 vaccine in SOT recipients.

METHODS

Adults (>18 years of age) from the Multi-Organ Transplant Program at the University Health Network (University of Toronto, Toronto,

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TABLE 1
Seroconversion of solid-organ transplant patients administered adjuvanted pandemic H1N1 (pH1N1) vaccine

Patient	Sex	Age, years	Primary disease	Type of transplant	Interval from transplant to vaccination	Immunosuppressive regimen	pH1N1 titre pre- and two and four weeks postvaccination	Brisbane H1N1 titre pre- and two and four weeks postvaccination
1	Male	53	Hepatitis C virus cirrhosis	Liver	Two months	Cyclosporine	1:10*	1:10*
						Mycophenolate mofetil	1:20†	1:20†
						Prednisone	1:20‡	1:20‡
2	Female	50	IgA nephropathy	Kidney	15 years	Cyclosporine	1:10*	<1:10*
						Prednisone	1:10†	<1:10†
							1:10‡	<1:10‡
3	Male	49	Idiopathic pulmonary fibrosis	Lung	22 months	Tacrolimus	1:40*	1:10*
						Azatioprione	1:320†	1:20†
						Prednisone	1:320‡	1:20‡
4	Female	51	IgA nephropathy	Kidney	Nine years	Cyclosporine	1:10*	1:10*
						Mycophenolate mofetil	1:10†	1:10†
						Prednisone	1:20‡	1:10‡
5	Male	36	Cystic fibrosis	Lung	Three years	Tacrolimus	1:10*	1:40*
						Mycophenolate mofetil	1:10†	1:40†
						Prednisone	1:10‡	1:40‡

**Prevaccination titre; †Two weeks postvaccination titre; ‡Four weeks postvaccination titre. IgA Immunoglobulin A*

Ontario) were enrolled in a research ethics board-approved protocol. Patients from the outpatient clinic who had given their consent and who had undergone an SOT received one dose of the pH1N1 adjuvanted vaccine. Demographic data including sex, age, primary disease, type of transplant, time interval from transplantation to vaccination, immunosuppressive regimen, and titres to pH1N1 and Brisbane H1N1 prevaccination, and two and four weeks postvaccination were recorded for all patients. A single 3.75 µg dose of adjuvanted pHIN1 vaccine (Arepanrix, GlaxoSmithKline, Canada) was administered by deep intramuscular injection and the patients were subsequently followed. The vaccine was composed of inactivated, split influenza virus, containing antigen equivalent to A/California/7/2009 (H1N1) v-like strain (X-179A), with the preservative thimerosal and the adjuvant ASO3, a DL-alpha-tocopherol-based squalene and oil-in-water emulsion.

The evaluation of antibody serological status was performed with sera extracted from blood samples drawn from vaccinated SOT recipients and tested using hemagglutination inhibition (HAI) assay at baseline and at two and four weeks postvaccination. This test evaluated antibody titres against pH1N1 influenza strain A/California/7/2009-like and the 2008/2009 seasonal H1N1 influenza strain A/Brisbane/59/07 (Brisbane H1N1). HAI was performed at the Ontario Agency for Health Protection and Promotion (Toronto, Ontario) using 0.7% guinea pig erythrocytes and 4HA units of virus (10). Dilutions from 1:10 to 1:1280 were performed. Vaccine-related seroconversion was defined as a postvaccination titre of ≥1:40 for subjects who were seronegative prevaccination (a fourfold increase in postvaccination compared with prevaccination titre). Vaccine-related seroprotection was defined as the presence of an HAI titre of ≥1:40 with a subsequent fourfold rise in titre postvaccination.

RESULTS

The five SOT recipients evaluated had a median age of 50 years (range 36 to 53 years), and three were male. The median time post-transplant was three years (range two months to 15 years). All other patient demographic data (underlying disease, the time interval of vaccination post-SOT and antibody titres) are shown in Table 1.

The prevaccination pH1N1 titre was 1:40 in one lung transplant recipient, whereas in the other four recipients it was 1:10. Seroprotection was observed in only one SOT recipient, who had a titre of 1:40 at baseline and a titre of 1:320 at both two and four weeks postvaccination. In this case, the recipient was documented to have previous infection with pH1N1 and his immunossupressive regimen was tacrolimus, azathioprine and prednisone. Another lung transplant recipient, who did not achieve seroconversion to pH1N1, had the same titre to Brisbane H1N1 (1:40) at baseline, as well as at two and four weeks postvaccination. Of note, none of the patients were being treated for acute rejection at the time of vaccination or during the follow-up period of observation.

No substantial vaccination-related adverse events were noted among the SOT recipients at the follow-up visits.

DISCUSSION

In adult SOT recipients, seasonal influenza vaccine has been shown to be safe, although the majority of studies have demonstrated suboptimal immunogenicity, particularly in patients on augmented immunosuppression for rejection (14,15). In our small study, we also demonstrated a low rate of seroconversion (one of five patients) with pH1N1 adjuvanted vaccine. Others have observed seroconversion measured by HAI in 15 of 29 (52%) SOT recipients vaccinated with two doses of adjuvanted pH1N1 vaccine (16). Although three of five (60%) pediatric heart transplant recipients also achieved protective titres with two doses of the adjuvanted pH1N1 vaccine within 23 weeks of transplantation, these titres were measured at least four weeks after vaccination (range four to 18 weeks) (17). Perhaps, seroprotection should be routinely assessed sooner than four weeks after vaccination.

Potential factors that may influence seroconversion include the type and intensity of the immunosuppressive regimen used, the amount of time after transplantation at which vaccination occurred, the number of vaccine doses and concurrent treatment for possible underlying rejection (18). In our study, we observed that all patients taking mycophenolate mofetil (MMF) did not respond to the vaccine, but this observation is limited by the small sample size. Previously, in lung transplant recipients, MMF therapy was associated with poorer response to influenza vaccine compared with sirolimus (19). Among renal transplant patients, treatment with MMF significantly reduced the immune response to vaccination also (20,21). In addition, similar or better serological response has been described with sirolimus therapy compared with calcineurin inhibitors (19,22). However, trials involving larger patient numbers need to be performed to validate this observation.

The time after transplantation may be an additonal modifying factor for seroconversion. Nevertheless, Altamirano-Diaz et al (17) did not

find any influence of the time after transplantation on the development of seroprotection. Of note, however, others (23) have observed higher seroprotection rates with increased times to vaccination after transplant in pediatric liver transplant patients. Inability to reach seroconversion in the early post-transplant period may reflect the influence of more potent immunosuppressive regimens during this period (24).

The issue of the number of vaccine doses needed to produce seroconversion may be pertinent. A two-dose vaccination schedule recommendation was proposed in some jurisdictions for immunocompromised patients during the pH1N1 outbreak and has been studied in nonimmunocompromised individuals, with added immunogenicity observed in the elderly (25). The adjuvanted vaccine recommendations for immunocompromised individuals were not based on scientific evidence available in the literature. In Canada (12) and the United States (26), only one dose of the pH1N1 vaccine was recommended, whereas in Europe, a regimen of two consecutive doses was adopted (27). The benefit of extra doses needs to be substantiated in immunocompromised adults.

Madan et al (28) showed that in pediatric liver transplant recipients, the second dose did not improve the interferon-gamma response, which is directly related to seroprotection. In contrast, in hematopoietic stem cell transplant recipients, De Lavallade et al (29) showed an increase in response after the second dose of adjuvanted H1N1 vaccine from 43% to 73%, with 100% efficacy in preventing influenza. In SOT recipients, seroconversion was observed in 15 of 29 (52%) patients without extra benefit, despite use of a second dose (16). A low seroprotection rate of 32% was observed after just one dose in adult heart transplant recipients. However, in lung transplant recipients, one dose of H1N1 2009 monovalent AS03-adjuvanted vaccine showed good clinical effectiveness (30).

Finally, the type and intensity of immunosuppression may impact the development of seroconversion and seroprotection. We could not draw conclusions about these issues due to our small sample size.

Intradermal injection has been used on nonresponders to influenza vaccine in renal transplant patients (31,32). However, in lung transplant recipients, seasonal 2008/2009 influenza vaccine administered by this method showed a lower frequency of seroprotection compared with the intramuscular route. Another alternative is the development of new vaccines (33).

CONCLUSION

The present small study questions whether one dose of adjuvanted pH1N1 vaccine is able to provide seroprotection in SOT recipients. In addition, seroconversion may have taken longer to develop although others have measured HAI titres in the same time frame that we used (16,20,32). These results may prompt the necessity to assess other adjuvanted influenza vaccines thorough evaluation of the immune response to other vaccination regimens (eg, more than one dose) and by testing them in a larger number of patients. In the future, interferon-gamma production by influenza or other T cell response parameters should be evaluated following vaccination to assess alternative strategies to optimize immune response in this vulnerable population.

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