Immunogenicity and safety of two doses of AS03A-adjuvanted influenza A H1N1v 2009 vaccine in cancer patients on chemotherapy - VACANCE study

P. Loulergue[1], B. Rousseau[2], O. Mir[3], A. Krivine [4], S. Kotti[5], E. Viel[2], T. Simon[5], A. de Gramont[2], F. Goldwasser[3], O. Launay[1], C. Tou rnigand[2]

1. CIC de vaccinologie Cochin-Pasteur, Groupe Hospitalier Cochin Broca-Hôtel-Dieu, AP-HP ; Université Paris Descartes ; Inserm CIC BT505, Paris, France. 2. Oncology, Hôpital Saint Antoine, 3. Medical Oncology, Hôpital Cochin, 4. Virology, Hôpital Cochin, 5. Clinical Pharmacology, Hôpital Saint Antoine

Abstract

Background
Influenza vaccination is recommended to cancer patients undergoing chemotherapy, but vaccine coverage remains low. During the 2009 influenza pandemic, French recommendations were to vaccinate immunocompromised patients with two doses of adjuvanted vaccine. This study aimed to evaluate vaccine immunogenicity in cancer patients receiving chemotherapy.
Patients and Methods
VACANCE is a prospective open-label study that evaluated the immunogenicity and safety of two doses of AS03A-adjuvanted H1N1v vaccine in cancer patients receiving cytotoxic and/or targeted therapies. Serum haemagglutination-inhibited antibody titres against influenza A H1N1v were measured at days 1, 21 and 42, to estimate the proportion of participants with antibody titres ≥1:40 (seroprotection rate), the efficacy of seroconversion, and factors that increased the geometric mean titre.
Results
Sixty-five patients were included. At baseline, 5% of patients had vaccine-strain titres of specific HI antibodies that were ≥1:40. After one and two doses of vaccine, seroprotection rates were, respectively, 48% and 73%, and seroconversion rates were 44% and 73%. Vaccine-related adverse events were mild to moderate.
Conclusion
A single dose of AS03-adjuvanted A/H1N1 vaccine triggered a low immune response in cancer patients on chemotherapy depending on their treatment type and frequency. Two doses are needed for these cancer patients.

Background

• Influenza and influenza-associated infections are responsible for an increased mortality rate in patients with cancer compared to the general population.
• Influenza vaccination can significantly reduce morbidity and mortality in healthy subjects.
• Although immunogenicity is reduced in cancer patients, vaccination is recommended; however, only a low rate of influenza vaccination is performed in these patients. To date, the optimal timing for vaccination of patients receiving chemotherapy remains unclear: the immunogenicity of the influenza vaccine seemed to be increased when the vaccine was administered between courses of chemotherapy.

• In 2009, the circulation of the novel A/H1N1v influenza virus and its potential severity in immunocompromised patients led the French authorities to recommend two doses of adjuvanted H1N1v vaccine, with a 21-day interval between, for cancer patients receiving chemotherapy. **Recommendations were to vaccinate at least 7 days after last administration of chemotherapy with a first dose of adjuvanted H1N1v vaccine, followed by a second dose at 3 weeks later.**
• Because no data were available on immunogenicity in cancer patients treated with cytotoxic drugs and/or targeted therapies, we conducted a prospective study to evaluate the immunogenicity and safety of this new influenza vaccine in cancer patients receiving different chemotherapy schedules and/or targeted therapies. We focused on the type (cytotoxic vs. targeted treatment) and schedules of chemotherapy treatments (every 3 weeks, 2 weeks, weekly or continuously).

• **The main objective of the study was to assess the immunogenicity of one and two doses of an AS03A-adjuvanted H1N1v influenza vaccine.**
• Secondary endpoints were to evaluate the impact of frequency and type of chemotherapy on immunogenicity and to assess the vaccine's safety.

Patients & Methods

Study population
This prospective study was conducted in two teaching hospitals in Paris, France. Patients were grouped according treatment frequency:
- patients receiving chemotherapy every 3 weeks (group 3W),
- patients receiving chemotherapy every 2 weeks (group 2W),
- patients receiving chemotherapy weekly or daily (group C),
- and patients only treated with targeted therapies, whatever the periodicity (groupT).

Groups 3W and 2W received the first vaccine dose on day 7 of the chemotherapy, and the second dose 3 weeks later.

	Number of patients (%)
Total number of patients	65 (100)
Gender (male)	33 (50.8)
Patients in an adjuvant setting	16 (24.6)
Metastatic patients	49 (75.4)
First-line palliative treatment	11 (17.0)
Second-line palliative treatment	18 (27.7)
Third line and other palliative treatments	20 (30.7)
Location of primary cancer	
Colorectal cancer	28 (43.1)
Breast cancer	8 (12.3)
Pancreatic cancer	6 (9.2)
Oesogastric cancer	5 (7.7)
Ovarian cancer	3 (4.6)
Lung cancer	3 (4.6)
Soft-tissue sarcoma	3 (4.6)
Duodenal and ampulla cancer	3 (4.6)
Renal cancer	2 (3.1)
Endometrial cancer	1 (1.5)
Pancreatic neuroendocrine cancer	1 (1.5)
Prostate cancer	1 (1.5)
Carcinoma, undetermined primary	1 (1.5)
Type of anticancer treatments	
Receiving at least one cytotoxic drug	56 (86.2)
Receiving a monoclonal antibody	29 (44.6)
Receiving bevacizumab	22 (33.9)
Receiving a multiple kinase inhibitor	5 (7.7)
Treatment group	
Group 1 (3W): cytotoxic drug given every 3 weeks	12 (18.5)
Group 2 (2W): cytotoxic drug given every 2 weeks	36 (55.4)
Group 3 (C): cytotoxic drug given each week or given continuously orally	8 (12.3)
Group 4 (T): targeted therapy alone (monoclonal antibody or tyrosine kinase inhibitor)	9 (13.9)
Supportive care treatments	
GCSF use	12 (18.5)
Erythropoietin use	2 (3.1)

Study vaccine
• The study vaccine was Pandemrix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), a monovalent A/H1N1v inactivated influenza vaccine, containing the AS03A oil-in-water adjuvant.
• This pandemic vaccine was licensed for the 2009–2010 season and contained 3.75 µg of haemagglutinin antigen of the A/California/7/2009 (H1N1) strain.
• It was packaged in multidose vials and administered intramuscularly (0.5 mL).

Laboratory methods
Serological tests were performed in a centralized virology laboratory.
Antibody titres against H1N1v were tested by a haemagglutination-inhibition test on days 1 (D1), 21 (D21) and 42 (D42).
The titre of HI antibodies was defined as the reciprocal of the highest serum dilution that completely inhibited haemagglutination.

Immunogenicity assessment
Immunogenicity was assessed according to the criteria of the European Committee for Proprietary Medicinal Products:
• Seroprotection rate was defined as the proportion of subjects with a serum HI antibody of at least 1:40,
• Seroconversion rate was defined as the proportion of patients with a fourfold or greater increase in HI antibodies between baseline and day 21 or day 42,
• Seroconversion factor as the fold increase in HI antibody titre at post-vaccination.

Results

Immunogenicity:

• At baseline, only three (4.6%) patients had HI antibodies against the A/California/7/2009 (H1N1v) strain with titres of 1:40 or more, which may represent exposition to the A/H1N1v virus or *in vitro* cross reactivity.

• Seroconversion rates were 44.4% and 72.7% at D21 and D42, respectively, indicating the percentage of patients who had an immune response to the vaccine.

• Seroconversion factors were 4.71±3.8 at D21 and 8.5±3.9 at D42, representing the intensity of immune response to the vaccine in terms of a fold increase in antibody titre a

	Baseline ($N = 65$)	Post-dose 1 (day 21) ($N = 63$)	Post-dose 2 (day 42) ($N = 44$)
SPR, N (%)[a]	3 (4.6)	30 (47.6)	32 (72.7)
SCR, N (%)[b]	NA	28 (44.4)	32 (72.7)
Geometric mean titre ± SD	8.5 ± 1.9	40.5 ± 3.8	74.1 ± 3.4
SCF[c] ± SD	NA	4.71 ± 3.8	8.5 ± 3.9

D1 is the day of the first dose of vaccine, D21 is the day of the second dose of vaccine, and D42 the day of the last follow and last blood sample.
[a]SPR is defined as the percentage of patients with ana HI antibody titre ≥1 : 40 and represents the percentage of patients with humoral immunity against H1N1v influenza 1.
[b]SCR is defined as the percentage of patients with a D1 antibody titre <1 : 10, a D21 or D42 titre of ≥1 : 40, or a D1 titre ≥1 : 10, and at least a fourfold increase in D21 or D42 titre.
[c]SCF or the geometric mean rise is defined as the ratio of geometric mean titre at D21 or D42 versus D1 and represents the intensity of response to the vaccine in term of antibody titres.
SPR, seroprotection rate; SCR, seroconversion rate; SCF, seroconversion factor; SD, standard deviation.

Safety:
The vaccine was well-tolerated.
Safety data on D42 showed that mild and moderate adverse events occurred with the same intensity and frequency as on D21, and no severe reactions related to the study vaccine were observed

Vaccine safety on D21 ($N = 65$, missing data for two patients)

	Mild, N (%)	Moderate, N (%)	Severe, N (%)	Total, N (%)	Mean duration (days ± standard deviation)
Not related		1 (1.9) tooth infection	1 (1.9) progression of cancer leading to death	2 (3.8)	
Possibly or probably related					
Local reaction					
Any				18 (28.6)	4.9 ± 2.3
Pain at injection site	11 (17.4)	2 (3.2)	0	13 (20.6)	4.2 ± 2.0
Erythema	5.79	1 (1.6)	0	6 (9.5)	5.0 ± 3.4
Swelling	5.79	2 (3.2)	0	7 (11.1)	5.0 ± 3.4
Itchiness	1 (1.6)	0	0	1 (1.6)	3
Systemic reaction					
Any				10 (15.8)	2.5 ± 1.9
Fever (oral temperature >37°8C for ≥24 h)	3 (4.8)	0	0	3 (4.8)	2 ± 0
Myalgia	2 (3.2)	1 (1.6)	0	3 (4.8)	3.0 ± 3.5
Chills		1 (1.6)	0	1 (1.6)	1
Fatigue	3 (4.8)	2 (3.2)	2 (3.2)	7 (11.1)	2.4 ± 1.6

Data are the number of cases (%). Total for 'any reaction' may be lower than the total of all the adverse effects because one patient may present with several adverse events at the same time.
Not related: another cause of events is more plausible, and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the vaccine administration, and/or a causal relation is considered biologically implausible.

Subgroup analysis:
• Seroconversion at D21 was negatively associated with the 3W and 2W groups compared with the C and T groups (OR 0.17, 95%CI [0.05–0.62], p=0.007).
• By D42, there was no statistical difference in seroconversion rates between the four groups. Being aged less than 65 was positively associated with seroconversion at D42 (OR 6.42, 95%CI [1.2–34.2], p=0.029).

Discussion

This study, which evaluated the immunogenicity of vaccination against 2009 H1N1v in immunocompromised patients treated with anticancer drugs, showed that:

- immunogenicity of one dose of vaccine was globally low (seroprotection rate: 47.6%), especially in patients treated with cytotoxic drugs given every 3 weeks or every 2 weeks.

- a second dose of vaccine induced a higher level of immunogenicity (seroprotection rate: 72.7%).

There was no significant difference according to the primary cancer, nor the use of GCSF, throughout the population. It is difficult to say whether the lack of immunization response was related to the treatment itself or to its periodicity.

For group 3W patients, those receiving docetaxel had a lower seroconversion rate on D21 than patients receiving chemo-based platinum salts. For the 2W group, no patients receiving GemOx or gemcitabine FDR had become seroconverted by D21. In comparison, it seems that patients receiving LV5FU2 had mostly become seroconverted compared to 4 out of 11 patients receiving FOLFOX85, 0 out of 3 receiving FOLFIRI1, 0 out of 3 receiving FOLFOX100, and 1 out of 5 receiving FOLFIRI3. The second injection provided additional seroconversion for patients receiving FOLFOX85 and FOLFIRI3 Gem FDR.

The type of chemotherapy seems to affect the vaccinal response. However, these observations are limited by the small number of patients.

To summarize, the second dose of adjuvanted vaccine improved immunogenicity and was necessary to achieve adequate anti-flu protection. Age was also an important factor that needs to be taken into account before planning influenza vaccination for a cancer patient.

The optimal vaccination schedule against flu for patients receiving chemotherapy remains to be determined. Hence, patients in groups 3W and 2W achieved low seroconversion rates when vaccinated at D7 after chemotherapy administration. Whether earlier administration could result in enhanced immunogenicity should be investigated in further studies.

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