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Influenza Vaccine Pilot Study in Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions The FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study

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Background—Recent reports have detected an increase in the number of patients with acute coronary syndromes during the flu season. In addition, the World Health Organization recommended vaccination against influenza infection for the Southern hemisphere in the winter of 2001. We evaluated the preventive impact of vaccination on subsequent ischemic events in myocardial infarction patients and in subjects undergoing planned percutaneous coronary angioplasty.

Methods and Results—We included 200 myocardial infarction patients admitted in the first 72 hours and 101 planned angioplasty/stent (PCI) patients without unstable coronary artery disease, prior bypass surgery, angioplasty, or tissue necrosis, in a prospective, multicenter log during the winter season. Infarct patients received a standard therapy and were then randomly allocated in a single-blind manner to either a unique intramuscular influenza vaccination or a control group. Similarly, PCI patients were allocated to either vaccination or control groups. Combined end points (death, reinfarction, and rehospitalization for ischemia) were assessed at 6 months' follow-up. The first primary outcome, cardiovascular death, occurred in 2% of the patients in the vaccine group compared with 8% in the control group (relative risk with vaccine as compared with controls, 0.25; 95% CI 0.07 to 0.86; $P=0.01$). The triple composite end point occurred in 11% of the patients in the vaccine group compared with 23% in controls ($P=0.009$).

Conclusions—Influenza vaccination may reduce the risk of death and ischemic events in patients suffering from infarction and those recovering from angioplasty during flu season. This response could be related to a humoral immune response with positive consequences during flu seasons. (*Circulation*. 2002;105:2143-2147.)

Key Words: myocardial infarction ■ infection ■ immune system ■ atherosclerosis

In 1908, Sir William Osler suggested a link between infection and atherosclerosis.¹ Except for several isolated reports, his theory was largely ignored for most of the century. Nevertheless, several intriguing associations were noted in the epidemiology of coronary artery disease to suggest a potential infectious influence. For example, rates of myocardial infarction (MI) and cardiac death increase in the winter and after influenza epidemics.²⁻³

It was shown in 1978⁴ that germ-free chickens infected with a herpes virus quickly developed atherosclerotic lesions similar to human coronary artery disease. Hajjar et al⁵ extended the observation of increased cholesterol ester accumulation in human smooth muscle cells infected by herpes simplex virus. Minick and colleagues⁶ reported that immunization of chickens with a turkey herpes virus prevented the development of atherosclerosis.

There is also strong evidence to suggest that virus infection plays a role in restenosis after pulmonary transluminal coro-

nary angioplasty (PTCA). Symptomatic restenosis is a common complication of coronary angioplasty, occurring in nearly 15% of patients receiving stents. A recent study demonstrated that patients with positive titers for cytomegalovirus had a much higher rate of restenosis 6 months after angioplasty.⁷ Restenosis also correlated with high IgG but not IgM levels for the virus. In addition, there was no change in IgG levels between the initial angioplasty and follow-up angiography, suggesting a chronic rather than an acute infection after angioplasty.

Epstein and Speir^{8,9} offered an interesting theory explaining the role of cytomegalovirus in coronary restenosis that may also be important in systemic atherosclerotic development. In immunocompetent hosts, latent cytomegalovirus rarely reactivates with active replication; however, it may undergo an "abortive infection," where only immediate early viral gene products are produced. Later on, atherogenesis may be triggered by angioplasty and activation of the latent viral infection.

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TABLE 1. Baseline Demographic Characteristics for the Myocardial Infarction Population

Characteristics	Group A (Vaccine) (n=100)	Group B (Control) (n=100)
Age, y	64	66
Sex	65 (65)	73
STEMI	47 (47)	37 (37)
Anterior infarction	21 (21)	20 (20)
Lytics	13 (27)	12 (32)
Primary PCI	6 (13)	5 (13.5)
No lytics or PCI	28 (60)	20 (54)
Killip class I	92	92
Killip class II	8	7
Killip class III		1
NSTEMI	53	63
Early aggressive strategy	8 (15)	6 (10)
Early conservative strategy	45 (85)	57 (90)
Elevated isolated total CK (positives)	11	2
CK-MB (positives)	55	72
TnT (positives)	34	21
Both serum markers [MB+TnT] (positives)	18	14
Hypertension	56	33
Diabetes	20	19
Prior myocardial infarction	14	14
Current or former smoker	42	30
CABG or PCI	14	23

Values are n or n (%).

STEMI indicates ST segment elevation myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction.

Because viral infection was suggested to be involved in both MI and subsequent events after percutaneous interventions, we decided to test the potential effects of influenza vaccination in those patients with coronary heart disease.

Methods

This study was a randomized, prospective, multicenter, single-blind, parallel-group, controlled pilot study. The analysis comprised 2 different cohorts of patients, a clinical group including those patients with ST-segment elevation MI or non-ST-segment MI occurring during the previous 72 hours, and an intervention group of patients undergoing angioplasty/stenting. Recruitment began in May 2001 and was completed early in September 2001.

A total of 305 patients (204 suffering from acute ST-segment elevation MI or non-ST-segment elevation MI, and 101 patients for planned angioplasty) were included in the study from 6 care units in Argentina. At admission, 204 patients met the criteria for ST-segment elevation MI (84) or non-ST-segment MI (120) according to a new consensus statement.¹⁰ Of those included in the first 12 hours, 25 were treated with aspirin and lytics and 11 were treated with antiplatelets and primary percutaneous coronary intervention (Table 1). Non-ST-segment MI patients underwent an early percutaneous intervention (performed according to guidelines during the first 48 hours after admission) in 14 of the cases.

Myocardial Infarction Patients

MI patients were allocated to 2 groups. Group A received a single unique intramuscular vaccination containing 0.5 mL of A/Moscow/

10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and AB/Sichuan/379/99-like virus. Follow-up telephone visits were scheduled at 31 days and 6 months after treatment. Group B served as a control group.

Inclusion Criteria

Male or female patients >21 years of age with an episode of angina at rest lasting at least 20 minutes in the previous 72 hours were eligible for inclusion. Definite evidence of underlying ischemic heart disease was also required, as shown by ECG changes, such as ST-segment elevation or depression, transient ST elevation (<15 minutes) of ≥ 0.1 mV, or T-wave inversions in at least 2 contiguous leads, plus 2 consecutive values of cardiac enzyme elevation (total creatine kinase [CK] above upper limit of normal or CK-MB >5% of total CK), or troponin T levels above 0.1 $\mu\text{g/mL}$ detected at least 6 hours from the beginning of the chest pain. The Favalaro Foundation Institutional Review Board approved the study, and informed oral consent was obtained from all patients.

Exclusion Criteria

Patients with evidence of evolving hepatic or renal failure, congestive heart failure (Killip Class IV), terminal disease, or any impeding cause of follow-up, including contraindications of vaccination, were excluded from the study. Patients with prior vaccinations were also excluded.

PCI Stenting Group

The second group included 101 subjects with planned stenting angioplasty in 2 sites in Buenos Aires City. Before the procedure, 51 of them received a vaccination, and 50 were followed as a control group. Those with unstable coronary artery disease or prior bypass surgery, angioplasty, or tissue necrosis were excluded from this second study group.

Outcomes

The first primary outcome was cardiovascular death. The secondary outcome was the composite of cardiovascular death, nonfatal MI, or severe recurrent ischemia judged at a 6-month follow-up.

Definitions

Recurrent ischemia was defined as chest pain lasting at least 5 minutes with new ST-T changes in at least 2 contiguous leads (ST elevation or depression ≥ 0.1 mV and/or T-wave inversion) while the patient was receiving optimal medical therapy (2 anti-ischemic drugs plus aspirin). Severe ischemia (in hospital) was defined as stated above, prompting the decision to revascularize within 24 hours after the event.

Acute MI (AMI) was defined as any value of CK-MB that was above normal and equal to at least 5% of total CK or a total CK value at least twice the upper limit of normal reference range. Q-wave MI was defined as chest pain lasting 20 minutes or more, followed by the appearance of new significant Q waves (≥ 0.03 seconds) in at least 2 leads in the ECG.

Early aggressive strategy in the non-ST-segment elevation MI patient group was defined as immediate angiogram on admission, followed by angioplasty or coronary artery bypass surgery in the next 48 hours, as opposed to early conservative strategy aggressive medical management followed by nuclear stress test before hospital discharge.

If >1 end point was observed in the same patient, the prespecified protocol assigned the end point considered the worst in the following sequence: severe recurrent ischemia, MI, death. The triple composite end point was defined as death, acute MI, and rehospitalization for recurrent angina requiring coronary artery bypass surgery or angioplasty.

Statistical Analysis

Preliminary power analysis based on an expected 20% reduction of major events at 180 days in the treatment group indicated that close to 4000 patients would be required to achieve an 80% statistical

TABLE 2. PCI Group: Baseline Demographic Characteristics

Characteristics	Vaccine Group (n=51)	Control Group (n=50)
Age, y	64	63
Sex	37 (72)	35 (70)
Target vessels treated using stents		
Left anterior descending	23 (45)	25 (50)
Circumflex	18 (35)	14 (27)
Right coronary	14 (27)	16 (31)
Medical history		
Hypertension	30 (59)	34 (68)
Current or former smoker	24 (47)	33 (66)
Diabetes	8 (16)	6 (12)
Hypercholesterolemia	30 (59)	28 (56)
Medication at time of procedure		
Gp IIb/IIIa receptor antagonists	3 (6)	3 (6)
Aspirin plus clopidogrel	51 (100)	50 (100)

Values are n (%).

power to detect important differences between groups. Given the magnitude of this sample size and the lack of previous evidence of vaccination efficacy in terms of risk reduction, we decided to do a pilot study with 300 patients.

Variables were grouped as categorical and continuous. The primary combined end points were considered a dichotomous outcome. The comparison of categorical variables between the 2 groups was performed by means of the Mantel-Haenszel χ^2 statistic or the Fisher's exact test whenever the number of cells with expected values of <5 was $>20\%$. Continuous variables were compared with the Student's *t* test or the Satterwhaite's *t* test when applicable.

Statistical calculations were done with the SAS v8.2 statistical software (SAS Institute).

Results

There were no significant differences between the 2 groups with regard to age, sex, or markers of necrosis at baseline (Tables 1 and 2).

Primary Outcomes

Of the total 305 patients (204 assigned as MI patients and 101 to the PCI stenting group) recruited into the study, 4 failed to meet the inclusion criteria. The remaining 301 eligible patients were assigned to either vaccine therapy (n=151) or control (n=150) through the randomization process.

The first primary outcome, cardiovascular death, occurred in 2% of the patients in the vaccine group compared with 8% in control group (relative risk [RR] with vaccine as compared with controls 0.25; 95% CI 0.07 to 0.86; $P=0.01$). The triple composite end point rates (a composite of cardiovascular death, nonfatal MI, or severe ischemia) occurred in 11% of the patients in the vaccine group versus 23% in controls (RR

TABLE 3. Primary End Point Rate at 6 Months' Follow-Up

	Group A (n=151)	Group B (n=150)	RR	<i>P</i>
Death	3 (2)	12 (8)	0.25 (0.07–0.86)	0.01
Triple end point	17 (11)	34 (23)	0.50 (0.29–0.85)	0.009

Values are n (%) unless otherwise indicated.

TABLE 4. Primary End Point Rates at 6 Months' Follow-Up for Myocardial Infarction Patients

	Group A (n=100)	Group B (n=100)	RR	<i>P</i>
Death	2	8	0.25 (0.05–1.15)	0.05
MI	4	4	1.00 (0.26–3.89)	
Rehospitalization	4	12	0.33 (0.11–1.00)	0.03
Double end point	6	12	0.30 (0.20–1.28)	0.03
Triple end point	10	24	0.42 (0.21–0.83)	0.008

Values are n unless otherwise indicated.

with vaccine as compared with controls 0.51; 95% CI 0.30 to 0.86; $P=0.009$; Table 3).

Clinical Myocardial Infarction Cohort

No patient was lost during the follow-up at 180 days. Table 4 shows the results of the intent-to-treat analysis in the 200 eligible patients; in the control group the incidence of the triple end point was 10% versus 24% in the vaccine group ($P=0.008$; RR: 0.42 [0.21 to 0.83]). In terms of death, there were 2 events in the active arm versus 8 in the control group ($P=0.05$; 95% CI 0.25, 0.05 to 1.15; Table 4).

PCI Stenting Group

There were no significant differences between the 2 groups with regard to age, sex, and target vessels at baseline (Table 2). Table 5 shows the results of the intent-to-treat analysis. In the control group, the incidence of the combined end point rates was 15% versus 22% in the control group ($P=0.5$). Lower rates of MI and cardiovascular death were observed in patients receiving the vaccination (Table 5). No influenza disease was reported in either of the 2 groups of patients during the follow-up period.

Discussion

Viral infection was thought to be involved in both MI and subsequent events after percutaneous interventions. In agreement with the recommendation by the World Health Organization that people in the Southern hemisphere be vaccinated against influenza infection in the winter of 2001,¹¹ we decided to test the potential effects of influenza vaccination in patients suffering from coronary artery disease. In this influenza vaccine pilot study of 301 patients with acute MI and planned angioplasty, vaccination was associated with a statistically significant reduction of subsequent ischemic events in the clinical cohort.

TABLE 5. Primary End Point Rates at 6 Months' Follow-Up in PCI Stenting Group

	Vaccine Group (n=51)	Control Group (n=50)
Death	1	4*
MI	4	4*
PTCA or CABG	3	3*
Triple end point	8 (15)	11 (22)*

Values are n or n (%).

* P —Nonstatistically significant.

In the natural course of atherosclerosis, the damage to the endothelium is the basis of the most compelling theory on the pathogenesis of this process, the "response to injury" hypothesis, first proposed by Ross and Glomset in 1976.^{12,13} Modified several times, this theory builds on the initial ideas of Virchow and others and incorporates more recent evidence of cell-cell interaction and inflammation. Bacterial and viral infections may also stimulate an autoimmune reaction through molecular mimicry that prolongs a chronic inflammatory process through specific and nonspecific mechanisms.¹⁴ The understanding of the conditions that determine the contribution of innate and adaptive immune mechanisms to the pathogenesis of autoimmunity remains an unresolved issue. It is known that infected endothelial cells increase thrombin expression¹⁵ and decrease thrombomodulin expression. The secretion of von Willebrand factor¹⁶ and a reduction in prostacyclin production facilitate platelet adhesion. The most important factor in triggering coagulation may be the virus-induced secretion of the powerful coagulant tissue factor.¹⁷

Despite the often contradictory serological and pathological evidence, viruses offer several explanations for how infection may precipitate and accelerate atherosclerosis. Cox-sackie virus, as well as the herpes viruses, upsets normal cholesterol metabolism, decreasing cytoplasmic and lysosomal cholesterol ester hydrolytic activity and thereby facilitating cholesterol accumulation.¹⁸ Increased smooth muscle cell uptake of oxLDL appears to be mediated by a virus-induced upregulation of oxLDL scavenger molecules on the surface of smooth muscle cells.¹⁹ Herpes virus and cytomegalovirus may also directly change the normally anticoagulant endothelium to a procoagulant surface through interfering with the normal hemostasis.²⁰ Recently, influenza infection has been proved to promote macrophage infiltration in the artery wall.²¹

In the case of angioplasty, partial reactivation or "abortive infection" in postangioplasty arteries has been postulated as an important contributor of early restenosis. Therefore, an abortive infection with only limited viral activity can severely alter the host's cell cycle. To the best of our knowledge, there is limited information with regard to B lymphocytes, influenza infection, and the adaptive immune system in this field.

Linking infection to atherosclerosis has proved difficult. Small epidemiological studies with numerous confounding factors have offered conflicting results. Many of these microbes prove difficult to culture and lack adequate serological measurements.²² The present study did not address this question.

Marek's disease in chickens and, more recently, *Chlamydia pneumoniae* in rabbits have approached Koch's Principles for an infectious cause of disease. As it has been suggested,²³ Koch's Principles may not be entirely applicable in diseases where an infection initiates an autoimmune response or is dependent on certain human leukocyte antigen haplotypes for disease progression. The present study did not address this question.

In a recent publication, Naghavi et al²⁴ found an interesting association between influenza vaccination and ischemic heart disease. In this case-control study among patients with prior

infarction, the reviewed medical records in a population seen in the University of Texas-Houston during the influenza season of October 1997 to March 1998, showed that vaccination against influenza significantly reduced the risk of subsequent myocardial necrosis.

Limitations of the present study were the inability to confirm further influenza infection in the population studied, particularly in the control group, and to find whether those subsequent events were attributable to a higher rate of influenza infection, as well as the fact that this was not a large-scale clinical trial. Serological analysis was not performed because this was not the purpose of the present study. Conversely, this prospective design contributes to knowledge retrieved from previous retrospective studies with confounding bias, such as socioeconomic factors.

In acute ischemic patients, the antiviral treatment could attenuate, at least in part, some of the procoagulant phenomena.²⁵ Influenza might also contribute to a reduction in the endothelial fibrinolytic capacity.²⁶ In addition, this viral infection could reduce the immune response to *Chlamydia pneumoniae*,²⁷ an intracellular pathogen that has been investigated in relation to plaque rupture and atherosclerosis.²⁸ On the other hand, in the interventional cohort, this infective burden may also play a peculiar role.

Compared with peripheral T cells, a greater percentage of the T cells in atherosclerotic plaques are in a late stage of activation. In addition, a small population of atherosclerotic T cells expresses proliferating-cell nuclear antigen, as well as costimulatory receptors, indicating they are responding to antigen stimulation.²⁹ The nature of the stimulating origin is still unclear, although there is evidence for both autoimmune and infectious causes.

There are very few B cells in atherosclerotic plaques. Because spontaneous activation of B cells occurs infrequently, the number of cells activated to a specific antigen is negligible when not exposed to that particular antigen. Thus, humoral immune response after vaccination stimulus may reflect a rapid migration of committed B-lymphocytes.³⁰ An increased production of influenza virus-specific antibodies may be found in peripheral blood 1 week after vaccination, and this peak is concurrent with an increased capacity of neutralizing serum antibodies.³¹

To our knowledge, the present study is the first to test the use of prophylactic influenza vaccine during the acute phase of coronary artery disease and during planned angioplasty. We hypothesized that this data may induce the exploration of a nonspecific effect on general immune responsiveness, particularly in MI, by the vaccine.

Appendix

Steering Committee Members

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