

Influenza Vaccination: a New Indication of an Old Therapy?

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INFLAMMATION IN ISCHEMIC HEART DISEASE

During the last decade the importance of the role that inflammation plays in the pathogenesis of atherosclerosis and its complications has become evident. Inflammation occurs at all stages of atherosclerosis, from early binding of leukocytes to advanced stage lesion development and thrombotic complications. Numerous factors capable of modulating inflammation have been described, and among them are all the traditional risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, smoking), and others such as infections (*Cytomegalovirus*, *Helicobacter pylori*, *Chlamydia pneumoniae*, infections of the oral cavity).

The cells involved in atherosclerotic inflammation are circulating monocytes (which mature into macrophages on the inner artery wall) and lymphocytes. We now know that up to 20% of the cells in atherosclerotic plaque are polyclonal T lymphocytes that react to oxidized low density lipoproteins (ox-LDL). The presence of high levels of circulating ox-LDL antibodies suggests that B lymphocytes are also involved in the pathogenesis of inflammation associated with atherosclerosis. The immune response mechanism and modified LDL favor uptake of B lymphocytes and their contribution to foam cell formation, activation of the cascade complement, and consequently, amplification of the inflammatory response. The importance of the systemic humoral response is shown in studies that report a >3-fold increase in the incidence of fatty streaks and fibro-elastic plaque in splenectomized

mice versus intact mice. In the former, spleen reconstitution re-establishes defenses against atherosclerosis.¹

The links between infections and atherosclerosis are the immune defense cells. Infection activates monocytes and macrophages but also produces inflammation, which activates Th1 lymphocytes and Th2 lymphocytes. Th1 lymphocytes recruit other inflammatory cells (macrophages/monocytes, T lymphocytes) and Th2 lymphocytes activate B lymphocytes. Activated B lymphocytes and T lymphocytes prolong and enhance the autoimmune and inflammatory responses, which in turn produce atherosclerotic lesions.

However, despite the biological plausibility of this relationship between infections and atherosclerosis, the role of infections in the development of atherosclerosis remains controversial. It is accepted that to establish a reliable connection between an infection and an illness, a number of conditions must be met. In 1890, when Koch isolated and cultivated *Mycobacterium tuberculosis*, he established three essential conditions for a pathogen to be considered the cause of a disease: *a*) the microorganism must be present in all cases of the illness; *b*) the same microorganism must not be found in cases of other illnesses as a random pathogen; *c*) once the microorganism has been isolated in a specific patient and cultivated in a medium, it must trigger the disease again. Unfortunately, in the case of atherosclerosis these conditions are difficult to meet. The constraints include technological limitations, presence of microorganisms, asymptomatic infections, incubation periods, the multitude of pathogens involved, the genetic makeup of carriers and of the microorganism, latent or persistent infections, chronic inflammation and delayed diagnosis. All of these limit the specificity, potency, timing and nature of the relationship between the microorganism and atherosclerosis. Consequently, if Koch's conditions are difficult to meet in the case of atherosclerosis, how can we establish a causal

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relationship between the microorganism and atherosclerosis? In this context, research design and epidemiology are especially important.

RESEARCH DESIGNS THAT SHOW A CAUSAL RELATIONSHIP BETWEEN INFECTION AND ATHEROSCLEROSIS

Three patient-centered approaches to research design exist: epidemiological studies, based on the population or on patients with ischemic heart disease; pathological studies, in which the microorganism found in atherosclerotic plaque is identified; and intervention studies, based on treatment with antibiotics or vaccine.

Epidemiological studies of the relationship between the infection caused by a specific microorganism and atherosclerosis are severely constrained. Infections (*Chlamydia pneumoniae*, *Helicobacter pylori*, *Cytomegalovirus*, infections of the oral cavity) may be asymptomatic, so the exact moment of contact with the pathogen is unknown. Similarly, we may not be able to specify when the development of atherosclerosis is triggered because it is a long-term chronic disease which is usually asymptomatic until complications occur. This probably explains the controversy over results obtained from epidemiological studies. Excellent reviews of research into the relationship between these infections and atherosclerosis have been published. Several meta-analyses of prospective epidemiological studies obtained weak results indicating a <1.2% risk reduction among seropositive or seronegative patients.^{2,3}

Pathological studies center on the cultivation of microorganisms or the sequencing of atherosclerotic plaque,⁴ and *C. pneumoniae* is the agent studied in greatest detail. However, we must remember that *C. pneumoniae* is an intracellular microorganism found in macrophages. These white blood cells are not usually found within the artery wall unless a lesion exists. Consequently, the presence of *C. pneumoniae* does not imply that it is the cause of the lesion, as it may simply be an innocent bystander.

Interventional studies involve the administration of drugs to counter specific pathogens considered responsible for disease, or activation of the immune system by vaccines. Initially, studies with antibiotics recruited patients who were seropositive for a specific microorganism. Consequently, any resulting benefit could be attributed to the effects of the antibiotic or the anti-inflammatory effect of the drugs. Later studies included patients who were seronegative for the microorganism. Results were also favorable, suggesting that at least part of the benefit of the antibiotics was not related to the antibiotic effect itself. We have already

mentioned the roles played by lymphocytes and macrophages in the development of atherosclerosis. In this connection, it was reported some years ago that patients vaccinated against flu virus were at less risk of repeat cardiovascular events than patients not vaccinated,¹ according to data on the greater incidence of cardiovascular mortality during influenza epidemics.⁵ Recent studies have reported the impact of vaccination against influenza, pneumococcus, or modified LDL particles and the incidence of new cardiovascular events.⁶⁻¹⁰

In mice, immunization with *Streptococcus pneumoniae* produces high levels of circulating specific IgM antibodies reacting to ox-LDL, because it has epitopes similar to those on oxidized LDL particles. Consequently, the animals' plasma is less able to block the binding of ox-LDL with macrophages. This suggests that the immune response may have beneficial effects on atherosclerosis.⁶

In general, results obtained from studies of the administration of flu vaccine as a therapeutic strategy in ischemic heart disease show a reduction in the incidence of myocardial reinfarction. In a retrospective, controlled case study, Naghavi et al⁸ found a 67% reduction in risk for reinfarction in vaccinated patients. Nichol et al¹¹ evaluated the influence of flu vaccination on risk of hospital admission for coronary heart disease, stroke, pneumonia or flu in a cohort of >280 000 individuals aged >65 years. They found flu vaccination to be associated with a significant risk reduction for hospital admission (19%) and stroke (16%-23%). The overall risk of death was reduced by approximately 50%. However, Jackson et al found no significant difference in the incidence of new coronary events in a cohort of 1378 vaccinated patients with a history of myocardial infarction when compared to those not vaccinated.⁹

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, León de la Fuente et al¹² present data drawn from the FLUVACS database.¹³ FLUVACS was the first study that used prophylactic flu vaccination during the acute phase of ischemic heart disease in a prospective, randomized research design. This was a pilot study of a cohort of 301 patients with acute myocardial infarction (AMI) and angioplasty in which vaccination was associated with a statistically significant reduction in new ischemic episodes. Their report analyzes the effect of vaccination in different subgroups. In line with Nichol et al,¹¹ the authors conclude that the subgroups that most benefit from vaccination are patients >65 years of age, with AMI without ST-segment elevation, nonsmokers, with a TIMI risk score >6.

The findings of these studies are consistent with public health recommendations made over a number of years. In Spain, campaigns are launched annually to promote the vaccination of elderly people, especially

those with comorbidity. In the general population, widespread flu vaccination campaigns for higher-risk groups (patients with coronary heart disease or respiratory illness) reduce death and illness significantly. What is new in the results from the studies we have described here is the cardiological focus given to a therapeutic strategy that cardiologists had largely ignored because their attention was centered on an associated illness: ischemic heart disease.

Our knowledge of the pathophysiology of atherosclerosis has increased beyond belief in recent years. The discovery of the inflammatory mechanisms associated with atherosclerosis has enabled us to establish new therapeutic strategies to counter the inducers of inflammation. Thanks to developments in pathophysiology, we are beginning to understand the benefits of statin treatment beyond the lowering of cholesterol levels, of angiotensin inhibitors treatment, and PPAR α agonists. Among the possible pleiotropic effects of these drugs are reduced leukocyte adhesion, macrophage activation, metalloproteinase production and tissue factor synthesis, as well as reductions in the synthesis of other cytokines.

In the case of flu vaccines or vaccines with modified LDL particles, we do not yet have sufficient data to establish public health policies for the general population as part of the standard range of therapies in primary/secondary prevention of ischemic heart disease. However, these vaccines constitute a therapeutic option that cannot be ignored and that we will surely follow with great interest over the coming years.

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