Sudden Death in a Patient Without Heart Failure After a Single Infusion of 200 mg Infliximab: Does TNF-α Have Protective Effects on the Failing Heart, or Does Infliximab Have Direct Harmful Cardiovascular Effects?
To the Editor:

A phase II study to assess the side effects of Remicade (infliximab) in patients with cardiac insufficiency NYHA III-IV revealed 7 deaths due to worsening of cardiac insufficiency among 150 patients who had received 3 infusions of Remicade of either 5 mg/kg or 10 mg/kg. The pharmaceutical company warned doctors not to give Remicade to patients with heart insufficiency of the class NYHA III-IV.

Case Report

We report a case of sudden death 18 hours after a single infusion of Remicade in a patient without heart insufficiency. The patient, a 64-year-old man with classical rheumatoid arthritis refractory to anti-inflammatory and immunosuppressive treatment (he had received hydroxychloroquine, methotrexate, leflunomide, deflazacort, oral corticosteroids, and AINS) accepted to try infliximab, a monoclonal antibody inhibiting the biological activity of tumor necrosis factor-α (TNF-α). The patient complained of pain in the joints and shoulders, morning stiffness, fatigue, and depression. He had a bicuseral pacemaker implanted in 1994 for bradycardia but had neither anamnestic clues nor clinical symptoms or signs of heart insufficiency and/or angina pectoris. The ECG was morphologically normal with sinus rhythm and frequent intervention of the pacemaker. The C reactive protein was 200 mg/L, sedimentation rate 90 mm/h, and interleukin (IL)-8 152.1 pg/mL. TNF-α before infusion was normal (2.41 pg/mL N<6.3). The infusion of Remicade (dosage: 3.17 mg/kg in 250 mL NaCl 0.9%) was started at 10:00 AM and ended at 1:00 PM. During the evening after the infusion, the patient felt very well; for the first time since the beginning of his disease, he was free of pain. Thus, he wanted to go home on the same evening and celebrate the “miracle.” All vital signs and parameters were normal. The night nurse attendant spoke with the patient at 6:30 AM of the following morning, and he told her that he had slept very well. At 7:25 AM, he was found dead, lying on his right side, without any signs of abnormal movements, loss of urine, foam at the mouth or nostrils, or discoloration of the skin. There was still no rigor mortis and the skin temperature was diminished but warm indicating that the death had occurred between 6:30 AM and 7:00 AM. The autopsy excluded an organic cause of death (no myocardial infarction, no heart insufficiency, no pulmonary or cerebral edema, no rupture of an aneurysm, no pulmonary embolism, and no internal bleeding).

Discussion

The mechanism of aggravation of preexisting heart failure and death after Remicade infusions is unknown. Because TNF-α is increased in the serum, circulating monocytes, tissue macrophages, and myocardocytes in patients with chronic heart failure (together with other parameters of ventricular failure and/or low cardiac output), it has logically been implicated in the pathophysiology of congestive heart failure. TNF-α is known to be the cause of cardiac cachexia. Transgenic mice with overexpression of TNF-α develop myocardial inflammation, cardiac hypertrophy, and dilated cardiomyopathy.1 In sepsis, TNF-α is believed to stimulate oxidative stress in the failing heart.2 The acute hemodynamic effects of TNF-α are as follows: reduction in cardiac output, dP/dt, blood pressure, and mean circulatory filling pressure.3 Although these effects are deemed negative, no correlation was found between TNF-α, its soluble receptors, and left ventricular end diastolic volume and ejection fraction, or pulmonary wedge pressure.4

In contradiction to the paradigm of TNF-α being harmful, other studies reveal that TNF-α has a protective negative inotropic action on the failing heart and stimulates the production of heat shock proteins, which enable cells to survive transient stresses, such as ischemia.5 Injection of TNF-α improves survival of TNF-α-/- knockout mice infected with encephalomyocarditis virus in a dose-dependent manner by increasing viral clearance.6 It induces protein synthesis in cardiac myocytes through activation of the PI3-kinase-Akt/PKB pathway7 and promotes remodeling at the border of infarcted myocardial tissues.8 It induces inducible nitric oxide synthase (iNOS) in macrophages but not in myocytes. Chronic TNF-α exposure in congestive heart failure results in translocation of transcriptionally inactive p50 homodimers, which constitute an adaptive response to minimize the inflammatory consequences of TNF-α exposure.9 Anti-TNF-α treatment reduces TNF-α and IL-1β but not MCP-1 and IL-6.10 Unopposed or overexpressed IL-6 promotes cardiac injury by interrupting both the cytokine autoregulatory network and the viral clearance in the viral cardiomytis model.11

The 7 cases of death in patients with chronic heart failure and our 8th case of sudden death in a patient without heart failure should moderate the enthusiasm of those who promote anti-TNF-α treatment for congestive heart failure until the balance between harmful and protective effects of TNF-α on the failing heart are fully elucidated.

Whatever the issue, the 10 mg/kg dose of infliximab has the probability of being harmful in patients with class III-IV heart failure and should be avoided for now.

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