LETTERS

Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra

Pedro J Ruiz, Eliezer Masliah, Taylor A Doherty, Ai Quach, Gary S Firestein

Ann Rheum Dis 2007;66:422–423. doi: 10.1136/ard.2006.060541

We report a case of adult-onset Still's disease (AOSD) with rapid deterioration of cardiac function when treated with recombinant human interleukin (IL) 1 receptor antagonist. Pro-inflammatory cytokines such as IL 1 and tumour necrosis factor (TNF) have been implicated in the pathogenesis of cardiac dysfunction, partly because of their negative inotropic activities in vitro and in vivo.^{1–3} This concept led to clinical trials evaluating the utility of TNF inhibitors in patients with congestive heart failure. Surprisingly, TNF blockade considerably increased the incidence of cardiac death. On the basis of these observations, TNF inhibitors are usually discontinued in patients with cardiac dysfunction.^{4–5} However, there is no information on the risks of other cytokine inhibitors.

A 29-year-old woman with a 4-year history of AOSD was admitted with fatigue, hypotension and shortness of breath. Her disease was marked by spiking fevers, arthritis and abdominal pain. These symptoms were refractory to methotrexate and etanercept, and were controlled only with 20–60 mg/day of prednisone. Six months before admission, the patient developed dyspnoea on exertion and paroxysmal nocturnal dyspnoea. A transthoracic echocardiogram showed a 57% ejection fraction and a pulmonary arterial systolic pressure of 31 mm Hg. The study also showed no evidence of atrial septal defect or valvular abnormalities. A cardiac adenosine-methoxyisobutylisonitrile study showed normal left ventricular function and no evidence of ischaemia. Three months before admission, anakinra treatment was initiated at 100 mg/day, with complete resolution of fevers and abdominal pain, and her steroids were tapered to 10 mg/day.

On the day of admission, the patient noted chills, fever of 100.6°F and mid-epigastric discomfort with nausea and vomiting. Cardiac examination showed tachycardia, but no jugular venous distension, murmur, rub or gallop. Her lungs were clear to auscultation and percussion. She had mild oedema in both lower extremities.

Table 1 shows the laboratory values of the patient on admission.

Her urine analysis had 3–5 white cells, but leucocyte esterase or nitrites were not detected. Chest radiograph on admission showed a normal cardiac silhouette and no infiltrates or effusions. Electrocardiogram showed sinus tachycardia with short PR interval, low-voltage QRS and non-specific T wave abnormalities. A blood gas was consistent with mild metabolic acidosis.

In hospital on day 2, the patient had shortness of breath that progressed to cardiorespiratory failure. Despite intubation and resuscitation efforts, the patient died by the end of the second day at the hospital. Autopsy showed a dilated cardiomyopathy as the most probable cause of death. Histological evaluation of

Table 1 Laboratory values of symptomatic variables

Variable	Values	Normal range
HCO ₃ (mEq/l)	20	24–31
Lactate (mg/dl)	38.4	6.5–19.3
AST (IU/l)	315	10–45
ALT (IU/l)	202	10–45
Alkaline phosphatase (IU/l)	244	30–130
Total bilirubin (mg/dl)	1	<1.2
Lipase (units/l)	29	22–51
White cells	6100 (23% bands, 40% segs, 8% monos and 29% lymph)	
Haematocrit (%)	38.5	36–46
Haemoglobin (g/dl)	13	12–16

ALT, alanine aminotransferase; AST, aminotransferase.

Figure 1 Heart-biopsy specimens. (A, B) Haematoxylin and eosin staining of the biopsy specimens of the heart and showing mild disorganisation of fibres and vacuolisation consistent with ischaemia. (C) A section of the left ventricle showing focal area of wavy fibres consistent with ischaemia.

the heart showed signs of ischaemia but no evidence of myocardial infarction or viral myocarditis (fig 1). No pulmonary emboli were noted, although diffuse alveolar damage consistent with adult respiratory distress syndrome was observed. All cultures for bacteria and fungi, including lung and blood, did not grow organisms. The rest of the autopsy was unremarkable.

Our patient exhibited some evidence of myocardial and/or pulmonary dysfunction before the initiation of IL 1 blockade. It is possible that her AOSD-associated cardiac disease progressed despite excellent control of her other symptoms. Alternatively, experience with TNF inhibitors suggests that cardiac events can occur despite clinical improvement in the underlying inflammatory disease. Concluding that a similar adverse event profile accompanies IL 1 inhibition is speculative, and we cannot be certain that anakinra played a part in this patient's cardiac events. However, the course of this patient suggests that systematic collection of data to assess possible associations between IL 1 blockade and cardiac complications is important.

Authors' affiliations

Pedro J Ruiz, Gary S Firestein, Division of Rheumatology, Allergy, and Immunology, University of California at San Diego School of Medicine, La Jolla, California, USA

Eliezer Masliah, Department of Pathology, University of California at San Diego School of Medicine, La Jolla, California, USA

Taylor A Doherty, Ai Quach, Department of Medicine, University of California at San Diego School of Medicine, La Jolla, California, USA

Competing interests: None declared.

Correspondence to: Dr Pedro J Ruiz, Division of Rheumatology, Allergy, and Immunology, 9500 Gilman Drive, La Jolla, CA, 92093-0656, USA; pjrui@ucsd.edu

Accepted 30 October 2006

REFERENCES

- 1 **Dinarello CA**. Interleukin-18. *Methods* 1999;19:121–32.
- 2 **Panas D**, Khadour FH, Szabo C, Schulz R. Proinflammatory cytokines depress cardiac efficiency by a nitric oxide-dependent mechanism. *Am J Physiol* 1998;275(Pt 2):H1016–23.
- 3 **von Haehling S**, Jankowska EA, Anker SD. Tumour necrosis factor- α and the failing heart—pathophysiology and therapeutic implications. *Basic Res Cardiol* 2004;99:18–28.
- 4 **Anker SD**, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol* 2002;86:123–30.
- 5 **Chung ES**, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- α , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133–40.

A triple altered collagen II peptide with consecutive substitutions of TCR contacting residues inhibits collagen-induced arthritis

Zhong-Qiang Yao, Ru Li, Zhan-Guo Li

The collagen type II (CII) 263–272 peptide is a predominant T and B cell antigenic peptide in rheumatoid arthritis.¹ Crystallographic data showed that 263F and 264K of CII263–272 are mainly responsible for binding with HLA-DR, and that 267Q and 270K were the major T cell receptor (TCR)-contact residues.^{2–3} We have shown that the CII altered peptide ligand (APL) with individual or consecutive substitutions of the TCR-contact amino acids could inhibit T cell activation induced by wild-type CII peptide in the context of HLA-DRB1, among which the most potent T cell activation suppressor is sub268–270, in which the amino acids of wild-type CII263–272 at positions 268, 269 and 270 were substituted with glycine or alanine (FKGEQAGAGE, substitutions underlined).^{4–5} Collagen-induced arthritis (CIA) is induced by wild-type CII in susceptible rodent strains. It has been regarded as the best rheumatoid arthritis model.⁶ In this study, we examined whether sub268–270 could show inhibitory effect in CIA.

Arthritis was induced in female Lewis rats weighing 120–140 g. Each rat was injected intradermally with 200 μ g bovine CII emulsified with Freund's incomplete adjuvant. A booster immunisation with 100 μ g emulsified CII was given 7 days later.⁶ The treatment with APL was initiated 24 h after arthritis onset. APL (sub268–270) at a dose of 90 μ g was given intravenously once a week, with a total of three injections. The irrelevant peptide (EGKPGQEGKF) and phosphate-buffered saline applied at the same dose were used as irrelevant

Ann Rheum Dis 2007;66:423–424. doi: 10.1136/ard.2006.057927

Figure 1 Inhibition of arthritis in rats with collagen induced arthritis by treatment with APL sub268–270. The arthritis score in sub268–270 treated rats was much lower than that of phosphate buffered saline and irrelevant peptide from day 6 to day 21 ($n=8$, $p<0.01$). PBS, phosphate-buffered saline.