

- Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; **121**: 293–98.
- Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *Lancet* 2007; **370**: 1829–39.

## Non-specific immunomodulation in chronic heart failure

We read the results of the ACCLAIM trial (Jan 19, p 228)<sup>1</sup> and, although the trial failed to meet its primary endpoints, we are encouraged that researchers are exploring the immune system in congestive heart failure. However, we have reservations about the method used in this trial and believe the conclusions (based on sub-analysis data) could prove erroneous.

The concept that a small volume of autologous, apoptotic leucocytes injected into the gluteus maximus would systemically skew the immune response from inflammatory to anti-inflammatory seems unlikely. Guillermo Torre-Amione and colleagues base their theory on in-vitro work reporting that the immune system secretes anti-inflammatory cytokines after interaction with apoptotic cells. Yet apoptosis occurs 50–70 billion times per day without immunomodulatory effect. Moreover, apoptosis acts as a regulatory mechanism during propioidicidal regulation,<sup>2</sup> via induction of tumour necrosis factor  $\alpha$ ,<sup>3</sup> or during passive withdrawal.<sup>4</sup> These mechanisms are not associated with skewed anti-inflammatory responses.

Furthermore, induced stress causes abnormal cell death rather than programmed cell death. This abnormal cell death results in stress protein expression and intracellular protein release, leading to inflammatory (rather than anti-inflammatory) pathways.<sup>5</sup> These issues are applicable to the ACCLAIM study, where cell stress

was rapidly induced via ultraviolet light and oxidative stress.

Research into immunomodulatory treatments for congestive heart failure has been stimulated after reports of elevated cytokine concentrations in patients with this disorder. This discovery has led researchers to attempt to control cytokine activity, rather than to understand the specific immunological mechanisms involved within the disease. We believe a great deal more research is required before successful immunotherapy for CHF is realistically achieved.

We declare that we have no conflict of interest.

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- Torre-Amione G, Anker SD, Bourge RC, et al. Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomised trial. *Lancet* 2008; **371**: 228–36.
- Boehme SA, Lenardo MJ. Propioidicidal apoptosis of mature T lymphocytes occurs at S phase of the cell cycle. *Eur J Immunol* 1993; **23**: 1552–60.
- Zheng L, Fisher G, Miller RE, et al. Induction of apoptosis in mature T cells by tumour necrosis factor. *Nature* 1995; **377**: 348–51.
- Jones LA, Chin LT, Longo DL, et al. Peripheral clonal elimination of functional T cells (1990) *Science* 1990; **250**: 1726–29.
- Matzinger P. Tolerance, danger, and the extended family. *Annu Rev Immunol* 1994; **12**: 991–1045.

The immunomodulatory treatment used in Guillermo Torre-Amione and colleagues study<sup>1</sup> (the Celacade system) is an expensive approach based on intramuscular injection of a 10 mL autologous blood sample treated with an excessive dose of ozone, ultraviolet light, and heat (42–5C) for 20 min and then given by intragluteal injections at several points during no fewer than 22 weeks. The extremely high oxidation of blood with ozone and ultraviolet light, and the additional heating, causes a denaturation of blood that contrasts with the practice of ozonated minor autohaemotherapy<sup>2</sup> and has proved useless in an AIDS trial<sup>3</sup> and in the

previously halted phase III Simpatico trial.<sup>4</sup>

Proponents of Celacade favour the concept that, after intramuscular administration of denatured blood, immune modulation ensues, with upregulation in the production of anti-inflammatory cytokines such as interleukin 10 and transforming growth factor  $\beta$ . Because chronic heart failure and limb ischaemia are disorders linked to inflammation and chronic oxidative stress, the reduction of proinflammatory cytokines is assumed to downregulate chronic inflammation and delay the progress of disease. I dissent from this interpretation because the biological and clinical effects of judiciously small ozone doses in vasculopathies are based on other crucial phenomena such as vasodilatation, increased delivery of oxygen in ischaemic tissues, and upregulation of antioxidant enzymes, especially haem oxygenase 1.<sup>5</sup> Immunomodulation might be only an additional factor.

The use of a masked saline placebo is also objectionable: it would have been more appropriate to use oxygenated autologous blood.

We declare that we have no conflict of interest.

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- Torre-Amione G, Anker SD, Bourge RC, et al. Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomised trial. *Lancet* 2008; **371**: 228–36.
- Bocci V. The case for oxygen-ozone therapy. *Bxci* 2007; **64**: 44–49.
- Garber GE, Cameron DW, Hawley-Foss N, et al. The use of ozone-treated blood in the therapy of HIV infection and immune disease: a pilot study of safety and efficacy. *AIDS* 1991; **5**: 981–84.
- Olin JW, Hiatt WR, Mohler E, et al. A multicenter, randomized, double-blind, placebo-controlled study of immune modulation therapy in patients with symptomatic peripheral arterial disease: the SIMPADICO Trial. Presented at the American College of Cardiology 55th Annual Scientific Session; March 11–14, 2006; Atlanta, GA, USA.
- Bocci V, Aldinucci C, Mosci F, et al. Ozonation of human blood induces a remarkable upregulation of heme oxygenase-1 and heat stress protein-70. *Mediators Inflamm* 2007; **2007**: 26785.



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