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Elsevier Editorial System(tm) for Atherosclerosis
Manuscript Draft

Manuscript Number: ATH-D-10-00143R1

Title: The irrationality of a non-specific immunomodulation therapy used in cardiovascular diseases deserves a critical comment.

Article Type: Commentary

Keywords: Keywords: Oxidative stress; Ozonetherapy; Chronic Heart Failure; Immunomodulation Therapy; Chronic Limb Ischemia

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Manuscript Region of Origin: ITALY

The irrationality of a non-specific immunomodulation therapy used in cardiovascular diseases deserves a critical comment.

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In 1997, Bulmer et al. [1] proposed a new procedure consisting in placing 10 mL of anticoagulated (+ 2 mL sodium citrate) of the patient's venous blood in a VC7000A system (Celacade™, Vasogen Inc, Mississauga, ON, Canada) where it was exposed to an oxygen/ozone gas mixture (ozone concentration 15.35 g/m^3) delivered into the blood at a flow of 240 mL/min and UV light (253.7 nm) at a temperature of 42.5 °C for about 20 min. The treated blood sample was removed from the system and immediately administered by intragluteal injection to the donor patient. Two treatments were given on consecutive days, followed by a third on day 14. Subsequent treatments were given at 4 week (28 days) intervals for at least 22 weeks, for a total of 8 injections.

The procedure uses an expensive device able to deliver an enormously toxic dose of ozone (107.5 mg per mL of blood) plus an undetermined UV irradiation at 42.5 °C. The final ozone dose is about 15000-fold higher than the average ozone dose used during the classical ozonated autohemotherapy [2] and the extremely high oxidation of blood causes a complete denaturation of blood components [3]. This procedure was invented aiming to establish a non-specific immunomodulation therapy (IMT) in the hope of reducing the inflammatory process and the chronic oxidative stress present in vascular disease. It has proved to be useless in an AIDS trial [4] and in a multicenter, randomized, double-blind, placebo-controlled study in 533 patients with symptomatic peripheral arterial disease (PAD), called the SIMPADICO trial [5]. It is most important noting that this trial had to be stopped three months early because it did not show any improvement in PAD and caused a significantly higher rate of malignancies in the IMT group [6]. Although in a pilot study [7] of 73 patients with heart failure the IMT seemed to result in a reduction of mortality, a subsequent multicenter study in 2426 patients [8], called the ACCLAIM trial, in chronic heart failure resulted in a "disappointing" results. In this trial no particular cancer predominated "although an imbalance was seen in reports of colorectal cancer (nine patients in the IMT group and three in the placebo group). The proponents of IMT [1,9] support the concept that after the IM administration of heavily denatured blood, an immune modulation ensues with an up-regulation in the production of the anti-inflammatory cytokines such as IL–10 and TGF-β and inhibition of proinflammatory cytokines, such as TNF-α,

IL-1 and IL-6. As chronic heart failure and limb ischemia are affections linked to inflammation and chronic oxidative stress, in theory the reduction of proinflammatory cytokines may down-regulate chronic inflammation and delay the progress of the disease. However, the previous failure of the SIMPADICO trial not only was a premonition of poor result in chronic heart failure but suggested that a strong immune suppression may favour neoplastic growth. Sliwa and Ansari [10] pointed out several potential problems but did not comment the wrong oxidative technology. An intermediate position of wait and see has been concurrently adopted by Sporter [11]. On the other hand, one of us [12,13] made specific criticism regarding the irrational technology and deeply dissented with Vasogen's (since October 2009 merged in IntelliPharmaceutics International Inc.) hypothesis. After two decades of studying the mechanisms of action in blood, reviewed in [2], the therapeutic range of ozone as a medical drug (0.21 ÷ 1.68 mmol/mL of ozone per mL of anticoagulated blood) has been defined. Ozone is a most reactive gas and inherently toxic but, if judiciously used, it is very useful in vasculopathies because it enhances vasodilation, it increases the delivery of both oxygen and growth factors in ischemic tissues and it does up-regulate several antioxidant enzymes and above all of heme-oxygenase-I [14]. Immunomodulation may be only a small additional factor. The misinterpretation of the real mechanisms of action and the obstinate use of a wrong approach can explain the "disappointing" results and the previous failure in treating chronic limb ischemia in the SIMPADICO trial [5,6]. Moreover a randomized clinical trial has proved the validity and safety of ozonetherapy in severe chronic limb ischemia [15]. For these reasons, believing that the procedure had been definitively entombed, we were surprised to read a recent paper by Marfella et al. [16] claiming that IMT may improve wound healing and limb salvage in patients with chronic limb ischemia. Although the same technology had been used, they obtained positive results absent in the SIMPADICO trial that was not cited in their paper. They also used a masked saline placebo in the control group where it would have been more appropriate to re-inject the untreated autologous blood. The reason of these controversial results remains unknown, unless there is a different reactivity between American and Neapolitan patients. One reasonable hypothesis may regard a

benevolent and unknown deficiency of the VC7000A system to deliver the excess of ozone. Moreover the authors, likely unaware that this immunosuppressive therapy may enhance tumorigenesis, have not checked this critical part and it should be suggested the need of exploring this aspect in their patients.

The reason of our concern is that the planned commercialization of such a device ought to be prohibited because practitioners may use this method in vascular patients unaware of the poor medical benefit and the risk of enhancing neoplastic growth.

The authors declare they have no conflict of interest.

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Point-by-point response

Regarding reviewer 1 we have objectively presented only the available reports.

Regarding the Associate Editor comment we have modified the text (highlighted in green) of our Commentary, clarifying only what is known and we have eliminated speculations.

***Statement of Originality**

The Authors declare the originality of the Commentary.