



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

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Corresponding Author: Prof. Velio Bocci,

Corresponding Author's Institution:

First Author: Velio Bocci

Order of Authors: Velio Bocci; Iacopo Zanardi; Valter Travagli

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1 The irrationality of a non-specific immunomodulation therapy used in cardiovascular diseases
2 deserves a critical comment.
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9 Velio Bocci^{a,*}, Iacopo Zanardi^b and Valter Travagli^b
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15 ^a Department of Physiology, University of Siena, Viale Aldo Moro 2, 53100 Siena, Italy
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18 ^b Department of Pharmaceutical Chemistry and Technology, University of Siena, Viale Aldo Moro
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21 2, 53100 Siena, Italy
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38 * Corresponding author at: Department of Physiology, University of Siena, Viale Aldo Moro 2,
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40 53100 Siena, Italy. Tel +39 0577234226. Fax +39 0577234219. E-mail: bocci@unisi.it (V. Bocci)
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1 In 1997, Bulmer et al. [1] proposed a new procedure consisting in placing 10 mL of anticoagulated
2 (+ 2 mL sodium citrate) of the patient's venous blood in a VC7000A system (Celacade™, Vasogen
3 Inc, Mississauga, ON, Canada) where it was exposed to an oxygen/ozone gas mixture (ozone
4 concentration 15.35 g/m³) delivered into the blood at a flow of 240 mL/min and UV light (253.7
5 nm) at a temperature of 42.5 °C for about 20 min. The treated blood sample was removed from the
6 system and immediately administered by intragluteal injection to the donor patient. Two treatments
7 were given on consecutive days, followed by a third on day 14. Subsequent treatments were given
8 at 4 week (28 days) intervals for at least 22 weeks, for a total of 8 injections.
9

10 The procedure uses an expensive device able to deliver an enormously toxic dose of ozone (107.5
11 mg per mL of blood) plus an undetermined UV irradiation at 42.5 °C. The final ozone dose is about
12 15000-fold higher than the average ozone dose used during the classical ozonated autohemotherapy
13 [2] and the extremely high oxidation of blood causes a complete denaturation of blood components
14 [3]. This procedure was invented aiming to establish a non-specific immunomodulation therapy
15 (IMT) in the hope of reducing the inflammatory process and the chronic oxidative stress present in
16 vascular disease. It has proved to be useless in an AIDS trial [4] and in a multicenter, randomized,
17 double-blind, placebo-controlled study in 533 patients with symptomatic peripheral arterial disease
18 (PAD), called the SIMPADICO trial [5]. It is most important noting that this trial had to be stopped
19 three months early because it did not show any improvement in PAD and caused a significantly
20 higher rate of malignancies in the IMT group [6]. Although in a pilot study [7] of 73 patients with
21 heart failure the IMT seemed to result in a reduction of mortality, a subsequent multicenter study in
22 2426 patients [8], called the ACCLAIM trial, in chronic heart failure resulted in a “disappointing”
23 results. In this trial no particular cancer predominated “although an imbalance was seen in reports of
24 colorectal cancer (nine patients in the IMT group and three in the placebo group). The proponents
25 of IMT [1,9] support the concept that after the IM administration of heavily denatured blood, an
26 immune modulation ensues with an up-regulation in the production of the anti-inflammatory
27 cytokines such as IL-10 and TGF-β and inhibition of proinflammatory cytokines, such as TNF-α,
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1 IL-1 and IL-6. As chronic heart failure and limb ischemia are affections linked to inflammation and
2 chronic oxidative stress, in theory the reduction of proinflammatory cytokines may down-regulate
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4 chronic inflammation and delay the progress of the disease. However, the previous failure of the
5
6 SIMPADICO trial not only was a premonition of poor result in chronic heart failure but suggested
7
8 that a strong immune suppression may favour neoplastic growth. Sliwa and Ansari [10] pointed out
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10 several potential problems but did not comment the wrong oxidative technology. An intermediate
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12 position of wait and see has been concurrently adopted by Sporter [11]. On the other hand, one of us
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14 [12,13] made specific criticism regarding the irrational technology and deeply dissented with
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16 Vasogen's (since October 2009 merged in IntelliPharmaceutics International Inc.) hypothesis. After
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18 two decades of studying the mechanisms of action in blood, reviewed in [2], the therapeutic range
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20 of ozone as a medical drug ($0.21 \div 1.68$ mmol/mL of ozone per mL of anticoagulated blood) has
21
22 been defined. Ozone is a most reactive gas and inherently toxic but, if judiciously used, it is very
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24 useful in vasculopathies because it enhances vasodilation, it increases the delivery of both oxygen
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26 and growth factors in ischemic tissues and it does up-regulate several antioxidant enzymes and
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28 above all of heme-oxygenase-I [14]. Immunomodulation may be only a small additional factor. The
29
30 misinterpretation of the real mechanisms of action and the obstinate use of a wrong approach can
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32 explain the "disappointing" results and the previous failure in treating chronic limb ischemia in the
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34 SIMPADICO trial [5,6]. Moreover a randomized clinical trial has proved the validity and safety of
35
36 ozonotherapy in severe chronic limb ischemia [15]. For these reasons, believing that the procedure
37
38 had been definitively entombed, we were surprised to read a recent paper by Marfella et al. [16]
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40 claiming that IMT may improve wound healing and limb salvage in patients with chronic limb
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42 ischemia. Although the same technology had been used, they obtained positive results absent in the
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44 SIMPADICO trial that was not cited in their paper. They also used a masked saline placebo in the
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46 control group where it would have been more appropriate to re-inject the untreated autologous
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48 blood. The reason of these controversial results remains unknown, unless there is a different
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50 reactivity between American and Neapolitan patients. One reasonable hypothesis may regard a
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1 benevolent and unknown deficiency of the VC7000A system to deliver the excess of ozone.

2 Moreover the authors, likely unaware that this immunosuppressive therapy may enhance
3 tumorigenesis, have not checked this critical part and it should be suggested the need of exploring
4 this aspect in their patients.
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10 The reason of our concern is that the planned commercialization of such a device ought to be
11 prohibited because practitioners may use this method in vascular patients unaware of the poor
12 medical benefit and the risk of enhancing neoplastic growth.
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18 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.