

Basophil Activation Test in Amiodarone Hypersensitivity and Non-IgE-Mediated Allergy

Vella A¹, Bjørklund G², Chirumbolo S^{2,3}

¹AOUI–University Hospital, Section of Immunology, Verona, Italy

²Council for Nutritional and Environmental Medicine (CONEM), Mo i Rana, Norway

³Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

J Investig Allergol Clin Immunol 2019; Vol. 29(5): 401-402
doi: 10.18176/jiaci.0416

Key words: Basophil activation test. CD63. CD203c. Amiodarone.

Palabras clave: Test de activación de basófilos. CD63. CD203c. Amiodarona.

To the Editor:

The recent article by Sánchez et al [1] investigated the fundamental role played by the application of a basophil phenotyping protocol including the CD123 and HLA-DR markers for electronically capturing cells in flow cytometry. The authors described 2 cases of immediate hypersensitivity to amiodarone that were successfully diagnosed using a CD123^{pos}/HLA-DR^{neg} gating protocol, with CD63 as the activation marker. Interestingly, the authors reported an increase in the CD63 percentage in peripheral blood samples treated with amiodarone 0.2 mg/mL, although the activation did not appear to follow a dose-response relationship. In the case of a purported anaphylactic reaction, CD63 upregulation increased by 37% (stimulation index, 5.11 [≥ 3]), while in the 84-year-old patient with no apparent allergy background but who was treated with antihistamine and corticosteroid therapy for itching and a red rash 15 minutes after taking amiodarone, CD63 upregulation reached 60% with a stimulation index of 30 [1]. The merit of this paper is that it shows the ability of the basophil activation test (BAT) to detect an allergic episode very early and to prevent the adverse effects associated with a skin prick test. We expected to observe a more pronounced CD63 response in the case of anaphylaxis in the 48-year-old patient, who also responded to the lowest doses of amiodarone (0.1 mg/mL), with a CD63 percentage of 14%-15%, while the second patient did not. Notwithstanding, the findings led to us raise some questions.

Basophils express A1 adenosine receptors, which are targeted by amiodarone [2,3]. The rapid up-regulation of the tetraspanin LAMP3, ie, CD63, is associated with a type of degranulation known as anaphylactic degranulation, which is also the mode used by a non-IgE-mediated basophil

response (as occurs for fMLP) some seconds after piecemeal degranulation [4]. Therefore, in the patient with the higher stimulation index for CD63, we may describe the event as a “threshold” effect of the amiodarone-mediated action on basophil A1 purinergic receptors, while for the anaphylactic patient we cannot exclude a real hypersensitivity mechanism. In these circumstances, as the phenotyping protocol is based on a panel of markers that excludes CD203c, the authors should select CD203c to determine whether their finding can be explained by a non-IgE-mediated mechanism [5]. It is well known that adenosine receptors in basophils downregulate cellular activation expressed via histamine release and the degranulation event, and it can be suggested that amiodarone, which dampens the sensitivity of A1 adenosine receptors, rapidly increases the anaphylactic degranulation mechanism of CD63 upregulation, resulting in the considerable CD63 percentage observed by the authors [1-3]. This speculation of ours seems to find some support in the evidence that the 84-year-old woman did not have a history of allergy to amiodarone. In the case of the 48-year-old man, however, who was clearly allergic to amiodarone, there was a dose-dependent increase in the CD63 percentage [1], with no threshold effects caused by mechanisms of receptor binding and recycling at some distance from the FcεRI/IgEs signaling pathway.

In conclusion, we would like to propose that the use of a BAT with a CD45^{dim}/CD123^{high}/HLA-DR^{neg}/CD63^{pos} protocol makes it possible to introduce 2 activation markers, ie, CD63 and CD203c, which may enable us to discriminate between an IgE-mediated response and a non-IgE-mediated response. In this paper, BAT emerges as a worthy tool for diagnosis of hypersensitivity and non-IgE-dependent immune responses to drugs. It should certainly be considered an essential tool in allergy diagnosis.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- Vílchez Sánchez F, Lluch Bernal M, González Muñoz M, Marques Mejías MA, Quirce Gancedo S, Cabañas Moreno R. Usefulness of basophil activation test in the diagnosis of amiodarone hypersensitivity. *J Investig Allergol Clin Immunol*. 2019 Apr 24;0. doi: 10.18176/jiaci.0404.
- Marone G, Findlay SR, Lichtenstein LM. Adenosine receptor on human basophils: modulation of histamine release. *J Immunol*. 1979 Oct;123(4):1473-7.

3. El-Ani D, Jacobson KA, Shainberg A. Regulation of A1 adenosine receptors by amiodarone and electrical stimulation in rat myocardial cells in vitro. *Biochem Pharmacol.* 1997 Sep 1;54(5):583-7.
4. MacGlashan D Jr. Expression of CD203c and CD63 in human basophils: relationship to differential regulation of piecemeal and anaphylactic degranulation processes. *Clin Exp Allergy.* 2010 Sep;40(9):1365-77.
5. MacGlashan D Jr. Marked differences in the signaling requirements for expression of CD203c and CD11b versus CD63 expression and histamine release in human basophils. *Int Arch Allergy Immunol.* 2012;159(3):243-52.
6. Sudheer PS, Hall JE, Donev R, Read G, Rowbottom A, Williams PE. Nicotinic acetylcholine receptors on basophils and mast cells. *Anaesthesia.* 2006 Dec;61(12):1170-4.

■ *Manuscript received May 7, 2019; accepted for publication May 13, 2019.*

■ **Salvatore Chirumbolo**

Department of Neurosciences, Biomedicine and Movement Sciences
University of Verona
Strada Le Grazie 9
37134 Verona (Italy)
E-mail: salvatore.chirumbolo@univr.it