

IgG4 does not induce an inflammatory reaction

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The reasonableness of IgG4 tests for the detection of IgG food allergies is the subject of controversial discussions in literature. As a consequence, there is widespread skepticism regarding the significance of these tests, in particular for IgG food allergies. ImuPro tests have been criticized as well. Yet one has to note that critical statements of several allergy associations as well as their position papers are mostly based on a paper by the European Academy of Allergy and Clinical Immunology (EAACI).

In discussing this topic, one has to quote the full title of the EAACI's paper: "Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report" (1). The other allergy associations' position papers are all based on this original publication. It is important to point out that the authors of the EAACI paper clearly address the use of IgG4 as inappropriate for detecting any kind of allergy. If one restricts it to IgG4, their statement is correct. Yet successive papers often mention IgG in general. This might be due to the fact that when allergists are talking about IgG they implicitly mean IgG4. Furthermore, IgE food allergy and IgG food allergy are often mixed up in public discussion. An IgE allergy (also called type I allergy) is the acute type, leading to immediate reactions even including an anaphylactic shock. An IgG food allergy (also called type III allergy) may lead to symptoms completely different from atopic allergy symptoms; they only appear some hours or up to three days after food consumption.

It is more than accepted by scientific societies that IgG4 differs from all other IgG subclasses and that IgG4 is the only IgG not inducing an inflammatory reaction. IgG is divided into four subclasses, IgG1, IgG2, IgG3 and IgG4. IgG4 is related to a type I allergy and can be considered the antidote of IgE. It does not opsonize the antigen and does not activate the complement (2). IgG4 is a scavenging antibody not inducing inflammation (3, 4). IgG1, IgG2 and IgG3 all have opsonizing properties and are able to activate the component, necessary for an inflammatory response (2). IgG4 is present in blood in much lower concentrations than the other subclasses.

The different ImuPro tests are neither testing for IgG4 nor are the tests addressing type I allergy. Therefore the allegations of allergy associations are false as they are all related to the use of IgG4. They are not applicable to ImuPro. 99 percent of IgG subclasses detected with ImuPro are IgG1, IgG2 and IgG3.



The publication from Jönsson et al. (5) showed and reproduced previous scientific findings that IgG can also be implicated in anaphylaxis. The assumption cited in past literature (which is also the basis of the arguments from allergists) that IgG represents a “normal” reaction with no clinical impact must be rejected. Jönsson et al. could show that neutrophils, IgG receptors and IgG were sufficient to induce an inflammatory cascade.

It is obvious that, once having passed the gut barrier, the reaction between an antigen and an antibody (IgG) will lead to the formation of an immune complex and that this immune complex will be destroyed by the immune cells, thus inducing an inflammatory reaction. If these immune complexes are destroyed in circulation, as part from some systemic impairment, no further symptoms will appear. If these complexes are fixed to a sensitized tissue - sensitized by a previous impact - the immune complexes are destroyed locally and may lead to chronically inflamed tissue, with related symptoms. The ImuPro tests identify potentially harmful food that could lead to a chronic inflammation which triggers other inflammatory processes in the body.

The new ImuPro concept comprises the notion of food challenge, thus identifying the clinically relevant trigger foods.

- (1) Testing for IgG4 against food is not recommended as a diagnostic tool: EAACI Task Force Report. Steven O. Stapel, R. Asero, B. K. Ballmer-Weber, E.F. Knol, S. Strobel, S. Vieths, J. Kleine-Tebbe *Allergy* (2008) 63:793-796
- (2) Immunologie, textbook Charles Janeway, Paul Travers, Mark Walport, Mark Shlomchick, Spektrum akademischer Verlag 5th edition (2002) 388-389 ISBN 3-8274-1079-7
- (3) Inhibition of complement activation by IgG4 antibodies. Van der Zee JS, van Swieten P, Aalberse RC. *lin. Exp. Immunol.* (1986) May: 64 (2):415-22
- (4) Immunoglobulin G4: an food antibody. Aalberse RC, Stapel SO, Schuurman J, Rispens T. *Clin Exp Allergy* (2009) 39 (4): 496-77
- (5) Mouse and human neutrophils induce anaphylaxis. Jönsson F, Mancardi DA, Kita Y, Karasuyama H, Iannascoli B, Van Rooijen N, Shimizu T, Daëron M, Bruns P. *J Clin Invest.* (2011) Apr 1;121(4):1484-96

