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Basophil Activation Test to Optimize the Diagnosis of Adverse Effects Following Immunization to Vaccines

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ABSTRACT

Adverse effects following immunization to vaccines (AEFI) are considered extremely rare events, the occurrence of which could gain a major role in optimizing allergy diagnosis by cellular tests. The urgent need to eradicate infectious diseases from population, is the main goal of vaccination campaign, therefore its successful outcome should be almost undisputable. Basophil Activation Test (BAT) is commonly used to ascertain a type I hypersensitivity reaction, often replacing reasability tests. Therefore, flow cytometry assay of basophil, as performed in BATs, is employed to test if a particular antigen elicits some activatory response from cells. The allergic subject may undergo an AEFI to vaccine not necessarily by an atopic reaction with an allergen within vaccines but because of the existence of an asymptomatic or not diagnosed inflammatory chronic allergy or other immune-disregulating allergy disorder in the subject. BAT, also in its basilar fashion, might be used from a simple heparinized whole blood specimen, but its application in diagnosing allergy before mandatory of facultative vaccination, must be associated to improve other diagnostic tools, at least in its pivotal application. If the application of BAT can be suggested to improve allergy diagnosis by introducing a cellular test in routinely used tools, such as sIgE and SPT, its use, due to possible expertise-consuming and relatively expensive issues, can be included in a specialized allergy consultancy panel as an exploratory approach of allergy inflammation, for which a subject undergoing immunization by vaccines is suggested to undergo and advised to sign an informed consent for BAT performing. This may extend BAT use in many other forms of chronic allergy and immunity disorders related to AEFI with vaccines.

Keywords: Adverse effects to vaccines; Allergy; Basophil; Basophil activation test; Flow cytometry.

INTRODUCTION

Adverse effects following immunization to vaccines (AEFI) are considered extremely rare events, the occurrence of which is often ascribed to anecdotal episodes that are difficult to relate to vaccination directly. Reported surveys on vaccine safety are therefore encouraging and vaccination campaign widely promoted.[1,2] Aside from rare cases of adverse effects reported in literature (Table 1), results from vaccine epidemiology should reassure people and reduce criticisms or complaints raised by public opinion. In Italy, for example, an animate debate about

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vaccine safety in the media[3-5] has led to pivotal studies aiming at rendering facultative mandatory vaccine in evolutionary age.[6] Health prevention strategies together with correct public information have a fundamental role in a vaccination campaign.[7] The urgent need to eradicate infectious diseases from population, is the main goal of vaccination campaign, therefore its successful outcome should be almost undisputable.[8-10] Ethical and socio-economic problems have raised several issues about mandatory vaccination, because it fosters substantial anti-vaccine sentiment, becoming counterproductive for human community; public claim for totally safe vaccines is quite impossible to fulfil, because of the possible occurrence [11] of adverse effects, though rare, and the inability to screen whole population undergoing vaccination. Politics and healthcare workers should cooperate to address possible costs and benefits related to the prevention and diagnosis of AEFIs. Official reports often show only short term or mild effects, rarely related to vaccination,[12-15] however unable to dampen some critical discussion elsewhere.[16]

Most of adverse effects come from hypersensitivity reactions due to component within vaccine or to vaccine interaction with subject's immune system. Pre-analytical tests before vaccination have become a concern in ethics and in health politics: for the many reasons, ethical issues are present at each stage in the vaccine product life cycle, the period extending from the earliest stages of research through the eventual design and implementation of global vaccination programs.[17] Actually, recent developments highlight fundamental principles of vaccine ethics and raise unique issues for ongoing vaccination activities worldwide.

In allergy, the role of a preliminary test to ascertain about the hypersensitivity to a forthcoming vaccination, raises some ethical, socio-economical and political issues, due mainly to the relative cost of proceeding in the assay performing and output interpretation, especially because of a time lag often occurring between vaccination and a putative vaccine-mediated adverse effect, leading often to simple anecdotal episodes.[18] From a biological point of view, allergy-related adverse effects do occur, although rarely, but most concern is focused only on anaphylactic reactions; however, vaccine-mediated anaphylaxis is rare.

Some clamour from worldwide community came about influenza vaccine just three years ago, due also to H1N1 pandemic influenza.[19]

In July 2009 the CDC Advisory Committee on Immunization Practices (ACIP) recommended use of the 2009-H1N1 vaccines.[20]

Adverse effects involving hypersensitivity to influenza vaccine, such as atopic dermatitis, asthma or anaphylaxis, resulted quite rare[21] but not totally excluded,[22] furthermore, some issues about egg-containing vaccine has generated discourse.[23-25]. A document providing updated guidance for the use of influenza vaccines in the United States for the 2011-2012 influenza season has been reported.[26] This example shows that incidence of vaccine-related allergy and anaphylaxis due to vaccination seems to be very poorly represented among population, based on the latest epidemiological and safety reports[10,27] and should not create any criticism.

Not with standing, routinely allergy diagnostic tools show many pitfalls and contradictory results when used to highlight an allergy onset or a clinical manifestation recalling a hypersensitivity reaction.[28] Diagnostic tools based only on anamnesis interview, serum IgE (sIgE) and/or skin prick tests (SPT) may be negative while basophil CD63 or other activation markers are suggestive of allergy inflammation.[29] In this context, basophil activation test (BAT) is widely used to assess an allergic reaction through a cellular *in vitro* assay; at the same time, it can be used to assess basophil function probing intracellular or membrane markers by flow cytometry, during inflammation in allergy. When, how and why BAT can be used in allergy diagnosis of AEFI? BAT is commonly used to ascertain a type I hypersensitivity reaction, often replacing reasability tests. Therefore, flow cytometry assay of basophil, as performed in BATs, is employed to test if a particular antigen elicits some activatory response from cells.

However, this is only one possible fashion with which BAT is introduced in allergy diagnosis.

The allergic subject may undergo an AEFI to vaccine not necessarily by an atopic reaction with an allergen within vaccines but because of the existence of an asymptomatic or not diagnosed inflammatory reaction as allergy in the subject. For example, egg-derived allergens may drive BAT application in its usual fashion for those vaccines (influenza, MMR, etc.) having possible egg-protein contaminants but AEFI have been reported also for children affected by classical food allergy (e.g. milk) and without symptomatic or diagnosed allergy to egg-proteins.[30] A similar evidence was reported by Kattan et al. in

Table 1. Some recently reported adverse effects following vaccination.

Vaccine	Adverse effect following immunization	Report	References
H1N1 influenza vaccine	a) Membranous glomerulonephritis	a) 1 case; 56-yrs old man, 23 day after vaccination	Kutlucan A et al, Indian J Pathol Microbiol. 2012 55(2):239-41
	b) Guillain-Barrè syndrome	b) Epidemiological survey	De Wals P et al JAMA 2012; 308(2); 175-81 Lehman HC et al, 2010; 10(9):643-51
HPV vaccine	Telogen effluvium	2 cases; 11 yrs old children	Tuccori M et al, Dermatology 2012, 224(3):212-4,
Smallpox vaccine	Neurologic ADR Eczema vaccinatum	Survey on Sejvar et al and Casey et al . reports Review	Schumm WR BMC Med 2006; 4:27 Reed JL et al. Clin Infect Dis 2012 54(6):832-40
Pneumococcal vaccine	Anaphylaxis	Case: 4th inj 23-valent vaccine	Ponvert et al, Vaccine, 2010; 28(52):6256-7
	Bullous pemphigoid		Valdivielso-Ramos et al An Pediatr Barc 2011;75(3):199-202
MMR vaccine	a) Reported different AEFIs	Epidemiological survey	Esteghamati A et al, Arch Iran Med 2011; 14(2):91-5
	b) Allergy AEFIs	Case report	Patia A et al, Pediatrics 2001; 10782):e27 Kamin W et al, Klin Pediatr 2008;
	c) Anaphylaxis	Case report	218(2):92-4 Novadzki IM et al, Allergol
	d) Hypersensitivity reactions		Immunopathol (Madr) 2010; 38(6):341-3
Hexavalent	Bullous pemphigoid	Case report	Valdivielso-Ramos et al An Pediatr Barc 2011;75(3):199-202
Meningococcal	Bullous pemphigoid	Case report	Valdivielso-Ramos et al An Pediatr Barc 2011;75(3):199-202
DaTP	Anaphylaxis	Case report	Kattan JD et al J All Clin Immunol 2011; 128(1):215-8

AEFI: Adverse effects following immunization to vaccines; HPV: human papilloma virus; ADR: adverse drug reactions; MMR: measles, mumps, rubella; DTaP: diphtheria, tetanus, persussis

children with cow milk allergy who underwent DaTP vaccination.[31] This evidence shows that a vaccine administered in an allergic subject (food allergy, drug hypersensitivity and so forth) may result in possible AEFI, an issue that claims for a more accurate allergy diagnosis in care units.

The role of basophils has been assessed as initiators in chronic allergy and some critical example in the debate may be addressed by considering allergy asthma, which can be triggered by vaccine-related adverse effects.[32] The synthesis of allergen-specific IgE is required for the development of allergic diseases including allergic rhinitis and allergic asthma (patients), but many individuals with allergen-specific IgE do not develop symptoms (asymptomatic subjects). Differences may exist between asymptomatic subjects and patients, while the optimization of allergy diagnosis might address this issue. Whether the presence of allergen-specific IgE translates into clinical allergy most likely depends on a complex interplay of multiple factors, where basophils play an important role. These include a family history of atopy, the levels of total serum IgE and, allergen-specific IgE or IgG, epitope-specificity of IgE and their degree of polyclonality (mono- vs poly-sensitized), as yet unidentified serum factors, the balance of T regulatory cells (Treg) and Th1/Th2 cells, the polymorphisms of the high affinity receptor for IgE (FceRI) and other factors regulating the activation of FceRI-bearing cells. Asymptomatic subjects may be more often

Table 2. Possible allergic adjuvants or contaminants contained in vaccines and reported in AEFI(*).

Adjuvant or contaminant	Vaccine	AEFI report
Gelatin	MMR DTaP, influenza, varicella (Varivax)	De Wals P et al JAMA 2012; 308(2); 175-81 Leventhal JS et al Dermatitis 2012; 23(3):102-9 Sakaguchi M et al J All Clin Immunol 1997; 99(2):263-4
Egg protein	MMR, influenza	Yavuz ST et al Acta Pediatr 2011;100(8):e94-6
Aluminum hydroxide	Influenza	Yin Da P et al, Biomed Environ Sci 2011; 24(6):624-9; Lerner A Lupus 2012;21(2):231-8
Aluminum salts	DTaP, DTaP-IPV, DTaP-HepB-IPV, Hib, Hib/HepB, pneumococcal,	Leventhal JS et al Dermatitis 2012; 23(3):102-9 Heidary N and Cohen DE Dermatitis 2005; 16(3):115-20 Beveridge MG et al Pediatr Dermatol 2012;29(1):68-72
Formaldehyde	DTaP, DTaP-IPV, DTaP-HepB-IPV, Hib, Hib-Hep B, Hep B (Recombivax), influenza, meningococcal,	Leventhal JS et al Dermatitis 2012; 23(3):102-9
Neomycin	DTaP-IPV, DTaP-HepB-IPV, DtaP-IPV/Hib (Pentacel), influenza, MMR, smallpox, varicella	Leventhal JS et al Dermatitis 2012; 23(3):102-9 Heidary N and Cohen DE Dermatitis 2005; 16(3):115-20
2-phenoxyethanol	DTaP, DtaP-IPV/Hib (Pentacel)	Leventhal JS et al Dermatitis 2012; 23(3):102-9
Thimerosal	Influenza, meningococcal (MPSV4-Menomune)	Leventhal JS et al Dermatitis 2012; 23(3):102-9 Song BJ and Katial RK Curr Allegy Asthma Rep 2004; 4(6):447-53

(*) A list of vaccine adjuvants can be found in Grabenstein JD. ImmunoFacts: Vaccines and Immunologic Drugs – 2012 (37th revision). St Louis, MO: Wolters Kluwer Health, 2011. DTaP: diphtheria, tetanus, acellular pertussis; HepB: hepatitis B; IPV: intramuscular polio vaccine; Hib: Haemophilus influenzae B type; MMR: measles, mumps, rubella; MPSV4: strain of a meningococcal vaccine

mono-sensitized than patients who may be more often poly-sensitized. There are many unanswered important questions that need to be addressed in order to better understand how IgE sensitization translates into clinical allergy. In asymptomatic airway hyper-responsiveness,[33] the investigation of allergy by basophil activation could give further diagnostic suggestion better than sIgE or SPT.[34] However, in the asymptomatic form of non-ashmatic eosinophilic bronchitis (NAEB), sIgE and SPT do not correlate with BAT;[35] an increase in asymptomatic bronchial hyper-responsiveness in these subjects following food allergy has been reported [36], suggesting a fundamental role of BAT in allergy diagnosis. This evidence may expand the debate about AEFI, for example, when trivalent influenza vaccines are considered. Data on safety in adults or children with asthma (when diagnosed) are limited,[37] although influenza virus increases asthma morbidity and vaccination is ultimately advised.[38] These examples pertain with the fact that routinely used analytical tools to diagnose allergy may be less informative without introducing BATs.

Moreover, the involvement of basophil in immune disorders, besides atopic response, has been assessed in recent years. For example, much attention has been focused on the role of regulatory T (T_{Reg}) cells in autoimmunity. But, there is strong evidence that peripheral T-cell regulation has also a crucial role in the control of allergy.[39] The role of the basophil as an effector cell in allergy and in host defense (particularly to parasites) has long been recognized. However, recent advances advocate for the basophil as an immune-modulatory cell that can promote naïve CD4+ T cell commitment to Th2 cell differentiation. While this is in keeping with the concept that the basophil is important in an allergic environment, new discoveries suggest context of allergic disease. Therefore, CD63 or other markers can be up-regulated during basophil activation following an auto-immune disorder.[40] Auto-immune

disorders have been reported as possible vaccine-related adverse effects.[41] The activation of the basophil by autoreactive IgE-containing immune complexes serves to amplify the production of auto-antibodies and contributes to the pathogenesis of the auto-immune disease.[42] The participation of basophils in acquired immunity is probably broader than suspected. During their activation, basophils produce thymic stromal lymphopoietin (TSLP).[43] TSLP is now known to have wide-ranging impacts on hematopoietic and non-hematopoietic cell lineages, including dendritic cells, basophils, eosinophils, mast cells, CD4(+), CD8(+), and NK T cells, B cells, and epithelial cells. Recently, it is becoming increasingly clear that TSLP may induce blockade of TH1/TH17 responses and the promotion of cancer and autoimmunity,[44] thus confirming the role of cells involved in allergy in the onset of autoimmune diseases.[45] However, the role of TSLP in basophil involvement in auto-immune disease has to be confirmed; this is only a speculative suggestion but would introduce a possible new role of basophils in inflammatory reactions about AEFI.

Finally, not all allergies are IgE-mediated reactions. In an attempt to find reliable methods to investigate hypersensitivity reactions, histamine and sulfidoleukotriene release tests have long been introduced. However, relatively few comprehensive quality reports have been published so far. Upon challenge with a specific allergen, basophils not only secrete quantifiable bioactive mediators but also up-regulate the expression of different markers which can be detected efficiently by flow cytometry using specific monoclonal antibodies. Adjuvants in vaccines may trigger innate cell responses causing B-cell activation and autoimmunity[29,46] (Table 2). Allergy to these immune adjuvants may elicit an atopic adverse effect but also non-IgE mediated reactions, leading to basophil activation also without serological markers. The suggestion to use a cellular test, such as a BAT, should add new insights to the comprehension of allergy due to vaccination, thus ameliorating the diagnostic endowment in the hand of physicians; basophils are crucial initiators, rather than effectors, in the development of IgE-mediated, chronic cutaneous allergic inflammation, in delayed-type hypersensitivity (DHT) and in the onset of chronic allergy, as well as represent the only diagnostic tool for non-IgE mediated allergy. In BAT, a very small sample volume of heparinised whole blood is sufficient to perform a flow cytometry evaluation of basophil response to allergens.[29,47] The investigation of basophil activation may be carried out also by analyzing the behavior of activation markers following IgE-mediated and/or non-IgE mediated stimuli, non vaccine-related allergens, a procedure which can show differences compared to non allergic individuals,[47] then giving important insights for diagnosis of allergy-related inflammation. BAT, also in its basilar fashion, might be used from a simple heparinized whole blood specimen, but its application in diagnosing allergy before mandatory of facultative vaccination, must be associated to improve other diagnostic tools, at least in its pivotal application.

If the application of BAT can be suggested to improve allergy diagnosis by introducing a cellular test in routinely used tools, such as sIgE and SPT, its use, due to possible expertise-consuming and relatively expensive issues, can be included in a specialized allergy consultancy panel as an exploratory approach of allergy inflammation, for which a subject undergoing immunization by vaccines is suggested to undergo and advised to sign an informed consent for BAT performing. Outcoming results from this pivotal use of BAT, might be collected to assess the application of cellular test in allergy specialized consultancy units before vaccination. Safety programs and research have done much progress in recent years but the role of basophils should not be underestimated, in this context.

While people are widely informed about vaccine safety, e.g. regarding allergy side-effects, very few arguments are addressed about the close relationship between mild hypersensitivity reactions and autoimmune disorders, for example. Prevention starts with pre-analytical surveys based on better diagnostic approaches. Any case presents ethical challenges for public health policy-makers, scientists, physicians, and other stakeholders in their efforts to improve the health of individuals, communities, and nations through vaccination and therefore a further effort in this sense has to be encouraged.

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