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Drug Allergy (MJ Torres Jaén, Section Editor)

Hypersensitivity Reactions to Biologicals: True Allergy?

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Opinion statement

Biological agents are a growing class of drugs that have modified the treatment of multiple chronic immune-mediated and tumor diseases. Despite these positive aspects, some issues may exist during the treatment with biologicals such as an increased risk of infections as well as the occurrence of infusion reactions, which in some cases could be severe and life-threatening. Concerning infusion reactions, it is important that allergists recognize the symptoms and know their underling pathogenic mechanisms in order to perform a correct diagnosis. The safety profile of biologicals is negatively impacted by their immunogenicity, which leads to the production of specific anti-drug antibodies. Various types of anti-drug antibodies have been demonstrated, including the IgE isotype, classically responsible for type I hypersensitivity reactions. However, non-IgE anti-drug antibodies, mostly represented by IgG, may lead to infusion reactions through complement activation or, as clearly shown in animal models, involving FcγRIII, basophils, and macrophages. Of note, a proportion of infusion reactions are not antibody-mediated such as the so-called cytokine-releasing syndrome, which may be clinically indistinguishable from the classic antibody-mediated hypersensitivity reactions. Knowledge of pathophysiology of infusion reactions may enable a correct diagnostic work-up to be set up in reactive patients. In fact, both in vitro and in vivo tests are available for detecting anti-drug antibodies towards biologicals, although they have not yet been fully standardized. Taking into account the above concerns, for these diagnostic procedures, particularly in vivo testing, physicians should be equipped with specific allergological expertise, to overcome possible issues in this new and specific of clinical field.

Introduction

Biological agents (BAs) are approved drug therapies that have a positive impact on the long-term outcomes of multiple diseases, including inflammatory, autoimmune diseases, cancer, and genetic deficiencies [1]. Unfortunately, these medications may be involved in adverse reactions that can impair the patients' quality of life and may occasionally be life-threatening or lead to the interruption of treatment [2]. BAs display multiple product-related factors (large and complex structure, non-human or highly repeated sequences, aggregation, impurities, and glycosylation) that deeply contribute to unwanted immune response to the drug itself, which may negatively impact its safety. The unwanted immune response leads to the development of anti-drug antibodies (ADA) which have been associated with increased frequency of clinical adverse events (AE), such as infusion reactions [3]. Various types of ADA have been observed during biological treatment, mostly IgG, but also IgE, IgM, and IgA [4, 5]. Sustained production of IgG is involved in the majority of the adverse effects, such as ADA-mediated pure red cell aplasia during therapy with erythropoietin [6] or thrombocytopenia by ADA against thrombopoietin [7] and anaphylactic reactions [8•]. Biological-specific IgE has also been demonstrated to mediate immediate hypersensitivity reactions (HRs) [4, 9–11]. In addition, low affinity and early-stage transient IgM, capable of activating the complement system, has been reported with anti-TNF agonists [4].

Terms and definitions

Many terms and definitions referring to BA-induced AE, in particular those regarding the timing of reactions, have been in common use throughout the involved clinical and scientific research. Specifically, various authors may have defined the same terms in inconsistent ways, leading to confusing situations and making comparison between results from different studies difficult. Variability in the incidence of acute infusion reactions to BA is reported in literature, which may be the consequence of the broadness of the definition for infusion reactions. Generally, AE should be defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related, whereas, any AE caused by a drug are defined as an infusion reaction. The term allergic HRs refers to antibody- or cellular-mediated infusion reactions. Infusion reactions may be classified as local or systemic [12]. Local infusion reactions, which are induced by subcutaneous BA, are called injection site reactions (ISR). Lastly, acute infusion reactions occur during or within 1 h after infusion or within a few minutes after subcutaneous injection, whereas delayed reactions occur from 1 h to 14 days [13, 14].

Why are biologicals potentially able to evoke a specific immune response?

All the biologicals, including fully human proteins, have the potential to induce unwanted immune response that leads to the development of specific ADA. Chimeric monoclonal antibodies (mAbs) such as infliximab contain xenoantigenic sequences that are recognized as non-self epitopes and stimulate the immune response. Fully human and humanized mAbs have even been designed and produced to reduce the immunogenicity of biotherapeutics.

However, these fully human antibodies can induce a strong humoral immune response, too, because of the well-known ability of the immune system to produce anti-idiotype antibodies that are specific to the V region of other immunoglobulin molecules. For example, adalimumab has been described as inducing ADA in up to 70 % of patients suffering from rheumatoid arthritis (RA) [15] and about 16 % of RA patients treated with golimumab, another anti-TNFα fully human mAb, can develop ADA [16]. Also, therapeutic recombinant molecules, such as abatacept and etanercept, can elicit a specific antibody response in exposed patients [17, 18]. The immunogenicity of BAs is related to additional factors such as the pattern of glycosylation (in the case of cetuximab) or other post-translational modifications (deamidation and oxidation) of mAb [11, 19]. It is well known that extrinsic factors such as aggregates and adjuvant-like contaminants may influence immunogenicity. There is evidence that protein aggregation can result in enhanced immunogenicity. Although the precise immunological and biochemical mechanisms responsible are poorly defined, both T-independent and -dependent mechanisms may be involved [20]. The immunogenicity may also be influenced by the protocol of administration [8•, 21]. Specifically, the role of episodic administration of the drug in the induction of immunogenicity has been described. Additionally, the dose of anti-TNF used also appears to be linked to the drug's ability to evoke immunogenicity. Data obtained from clinical trials in RA patients showed that higher starting doses of infliximab are associated with higher serum drug levels and lower immunogenicity [22]. Concomitant therapy with non-biologic disease-modifying antirheumatic drugs—specifically methotrexate (MTX)—reduce the ADA occurrence [23•], although further studies are needed to define the specific regimens and doses of cotreatment with MTX able to reduce ADA formation (and potential for similar effects with other immunosuppressive therapy regimens).

Clinical manifestations of hypersensitivity reactions to biologicals

The clinical manifestations of both acute and delayed reactions may range from mild to severe and life-threatening events. For this reason, important clinical consequences such as interruption of the treatment or even the death of the patient may occur. Among acute infusion reactions, anaphylaxis, which can be defined as mild, moderate, and severe, according to Brown's classification [24], is the most severe event which may occur. Anaphylaxis may be characterized by respiratory involvement (laryngeal edema and bronchospasm) accompanied by urticaria, itching, abdominal pain, vomiting, diarrhea, and hypotension. Different pathogenic mechanisms underline immediate HRs, but clinical manifestations may be independent of that process. In other words, the same clinical sign or symptom may be induced by different mechanisms. In our experience with patients who developed an immediate HR to infliximab, a higher severity of reactions occurred in those who displayed an IgE-mediated event. Additionally, IgE-mediated HRs occurred very early during the course of treatment [8•]. The incidence of systemic delayed infusion reactions, which usually occur within the first 2 weeks after the administration of the BA, is lower than the acute events, and they include generalized maculopapular exanthema,

lychenoid or granulomatous exanthema, psoriasiform eruptions, acneiform eruptions, erythema multiforme, and Steven-Johnson's like syndrome [25]. In some cases, the clinical presentation of delayed reactions may be consistent with a classic serum sickness disease characterized by arthralgia, myalgia, exanthems, fever, urticaria, and itching [26]. Patchy lung infiltrates and skin necrotizing vasculitis may also be present, sustained by inflammatory infiltrates involving small blood vessels and complement deposition at immunofluorescence staining. Data from literature report that serum sickness-like reactions are developed in about 3 % of infliximab-treated patients [26], but the therapy with other chimeric molecules used to treat various conditions, such as rituximab for lymphoma, omalizumab for asthma, and natalizumab for multiple sclerosis, may be complicated by these reactions [26–29]. Regarding subcutaneously administered BA, the most common AEs are ISR, which are characterized by erythema, swelling, itching, or infiltrated plaques. ISR may occur within a few minutes (immediate reactions) or later (delayed reactions). Systemic reactions after subcutaneous BA are rare.

Pathogenic mechanisms of immediate hypersensitivity reactions

Antibody-mediated reactions

Immediate HRs to biologicals are closely related to the development of ADA, and different antibody isotypes may be involved in their pathogenesis. In particular, both IgE and non IgE-mediated mechanisms may be suggested [30]. In fact, using the CAP system, we showed that infliximab-specific IgE mAbs are detectable in about 30 % of patients who experienced an immediate HR [8•]. Data from literature have confirmed that IgE ADA is associated with immediate reactions induced by several other mAbs, such as tocilizumab, cetuximab, natalizumab, and muromonab [9, 10, 19, 31]. The positivity of skin testing at immediate reading confirms the biological activity of serum IgE ADA in the activation of mast cells [8•, 32]. Type I HRs do not usually occur during the first infusion of the BA, since the initial antigen exposure is required for sensitization. However, pre-existing BA-specific IgE antibodies have been described, as in the case of cetuximab, which shares some epitopes (galactose-α1-3-galactose) with mammalian proteins towards which some patients with meat allergy may be sensitized before the drug exposure. In these patients, severe HRs at first infusion of the drug have been clearly observed [11]. In a few cases of BA-related HRs, the pathogenic mechanism was sustained by IgE antibodies against additives that are present in the drug formulation. This finding has been described in some case reports for omalizumab and eritropoietin [33, 34]. From a cellular point of view, circulating drug-specific T cells with a clear-cut Th2 profile, and thus able to sustain the humoral IgE response, were detected in a patient who had experienced two severe anaphylactic reactions to rituximab, in association with drug-specific IgE in the serum and skin test positivity [35]. The majority of reactive patients test ADA positive but IgE negative thus suggesting that anaphylaxis may also occur in an IgE-independent manner. As demonstrated in murine models, specific IgG, FcγRIII, macrophages, basophils, and the platelet-activating factor may be the major mediators of anaphylaxis [36]. In addition, the development of IgG specific to biologicals may lead to complement activation with subsequent production of anaphylatoxins and then mast cell activation. In other words, IgG ADA can both directly and indirectly activate

circulating basophils and tissue mast cells. HRs to biologicals may be the most likely candidates for human IgG-mediated anaphylaxis (Fig. 1).

Non-antibody-mediated reactions

Among non-antibody-mediated reactions, the most well-defined condition is cytokine release syndrome (CRS) (Fig. 1), which may be clinically indistinguishable from type I hypersensitivity, as clinical manifestations of type I HRs and CRS may overlap, as mentioned above. However, CRS usually occurs during the first infusion, with mild to moderate symptoms, as in the case of rituximab, a chimeric IgG1 mAb directed to the CD20 molecule expressed by B cells. It is the result of massive cytokine release by different types of immune cells, including monocytes/macrophages, T cells, B cells, and NK cells. Both in vivo and in vitro experimental data indicate that TNFα, interferon (IFN)-γ, and IL-6 are the main mediators in CRS [37]. Multiple not mutually exclusive mechanisms are involved in the induction of CRS. For example, the cross-linking of mAbs bound to target cells (e.g., CD20+ cells), the subsequent complement activation, the lysis of target cells, and finally, the release of their

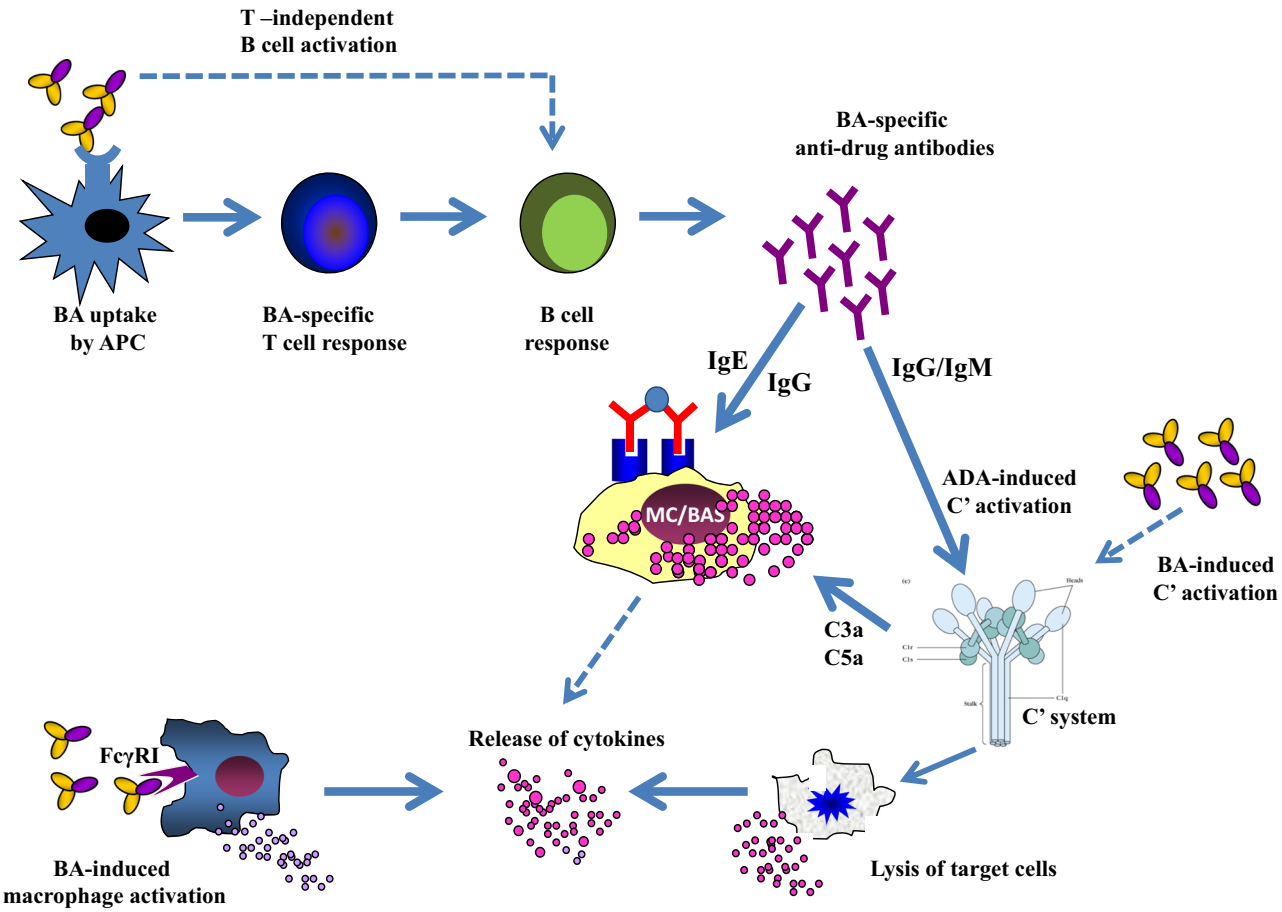

Fig. 1. Pathogenic mechanisms of immediate hypersensitivity reactions to biological agents. Both antibody and non-antibody-mediated mechanisms are shown. *ADA* anti-drug antibodies, *BA* biological agent.

cytokines and chemokines may occur. Additional effector cells (monocytes, macrophages, NK cells, and cytotoxic T lymphocytes) are then recruited by chemokines, thus leading to the amplification of the cytokine release. Furthermore, recruited macrophages, which express Fcγ receptor, are able to interact with the Fc portion of the mAb and then contribute to the release of cytokines. Finally, it is also likely that CRS and type I hypersensitivity response cannot be mutually exclusive, since mediators involved in CRS may be released by mast cells and basophils activated via FcεRI. In other words, CRS may amplify the classical IgE-mediated anaphylaxis. However, short-term interruption of the drug administration, reduction of infusion rate, and premedication with histamine blockers may be useful in the management of CRS, but not of type I HRs [38].

Pathogenic mechanisms of delayed hypersensitivity reactions

Serum sickness-like reactions appear to be associated with the presence of ADA, being related to the formation of complement-binding immune complexes (type III HRs), with subsequent immune complexes deposition, complement activation, and inflammatory infiltration around small vessels. In fact, immunofluorescence in the presence of complement deposition around vessels of skin specimens may be shown [39].
Thromboembolic events have been observed in about 5 % of patients treated with TNF antagonists [40]; in the case of adalimumab-related events, a correlation between ADA development and the occurrence of venous and arterial thrombosis has been reported [41]. However, other alternative mechanisms can be suggested, such as the development of antiphospholipid antibodies and the pro-inflammatory immunologic status that may characterize these patients. The pathomechanism of delayed disseminated skin reactions, even if not completely understood, are most probably sustained by the activation of specific cellular mechanisms, as suggested by results obtained in the analysis of two infliximab-induced maculopapular exanthemas [42]. Accordingly, a positive intracutaneous test at delayed reading (48 h) has been described in a patient with a maculopapular exanthema due to abciximab [43]. Some delayed disseminated skin reactions are a direct molecular target-dependent event. This is the case in cutaneous eruptions induced by epidermal growth factor receptor inhibitors [44] or in exacerbation of psoriasis [45] during TNFα antagonists.

Allergological work-up of immediate hypersensitivity reactions

In vitro tests

The immune response to biologicals should be evaluated by the analysis of serum ADA, by using a typical tiered assay strategy. In fact, all ADA-positive samples at the initial screening assay have to be further evaluated in a confirmatory test to rule out false-positive results. In addition, confirmed positive samples may be submitted to a further characterization to define the IgE isotype. A number of analytical formats and methods are available for the detection of ADA, including enzyme-linked immunosorbent assay (ELISA),

radioimmunoassay (RIA) or radioimmunoprecipitation assay, surface plasmon resonance, and electrochemiluminescence [46–48]. Advantages and limitations can be described for each of these formats. ELISA is the most frequently used assay to evaluate ADA development in treated patients. It is important to underline that the majority of these tests are sensitive to the effects of drug interference, because the presence of circulating drug leads to the formation of soluble immune complexes, resulting in false negative data. On the other hand, false positive results may occur due to cross-binding of IgG by rheumatoid factors or anti-hinge antibodies in the bridging ELISA format. Using the ImmunoCAP platform and other immunoassays, the presence of BA-specific IgE antibodies may be detected. However, the detection of specific IgE may be complex, due to the low concentration of these antibodies, in comparison to all other isotypes. Specifically, ADA IgG can considerably interfere with the detection of ADA IgE. Furthermore, other challenges in ADA IgE detection may be the fact that a proportion of these antibodies is bound to the FcεRI on mast cells and basophils and not in the serum.

In vivo tests

Although skin tests for BA have not yet been standardized due to the lack of concise information on specific test concentration, both prick and intradermal tests can be performed. Indeed, positive skin testing with biologicals has been described in patients who developed immediate reactions for several drugs, but the literature on skin testing for BA is still poor and the majority of data regards anti-TNF agents [4, 8•, 32, 35, 49, 50]. Skin testing, including the skin prick test (SPT) and intradermal test (IDT), is relatively simple to perform and usually shows good specificity for most drugs. Unfortunately, the sensitivity of skin testing is generally low. IDT has a higher sensitivity than SPT but also a higher risk of inducing irritant reactions leading to false positive results. Therefore, before advocating skin testing as a valid investigation method for HRs to BA, the non-irritant concentrations should be defined for each BA. Another open point is the definition of the interval between the occurrence of HR and the allergological evaluation, due to the undefined, but relatively fast, timing of skin testing negativization. In our experience, patients with reactions to infliximab and rituximab may represent a "clinical model" to show the usefulness of skin testing in the management of HRs, because a close correlation between ADA positivity, the presence of serum-specific IgE, and skin testing positivity has been demonstrated in reactive patients [8•, 35]. Skin testing may also be useful in identifying sensitized patients, among subjects that are clinically at risk for reactions, such as those who will be retreated after a period of interruption. Furthermore, no unexpected adverse reactions to skin testing were recorded in several published cases [8•, 32]. A suggested algorithm for the evaluation of immediate HRs to BA by allergists is reported in Fig. 2

Allergological work-up of delayed hypersensitivity reactions

In vitro tests

Cumulatively, there are very few data regarding the allergological tests for delayed HRs. The association of ADA development and the onset of delayed

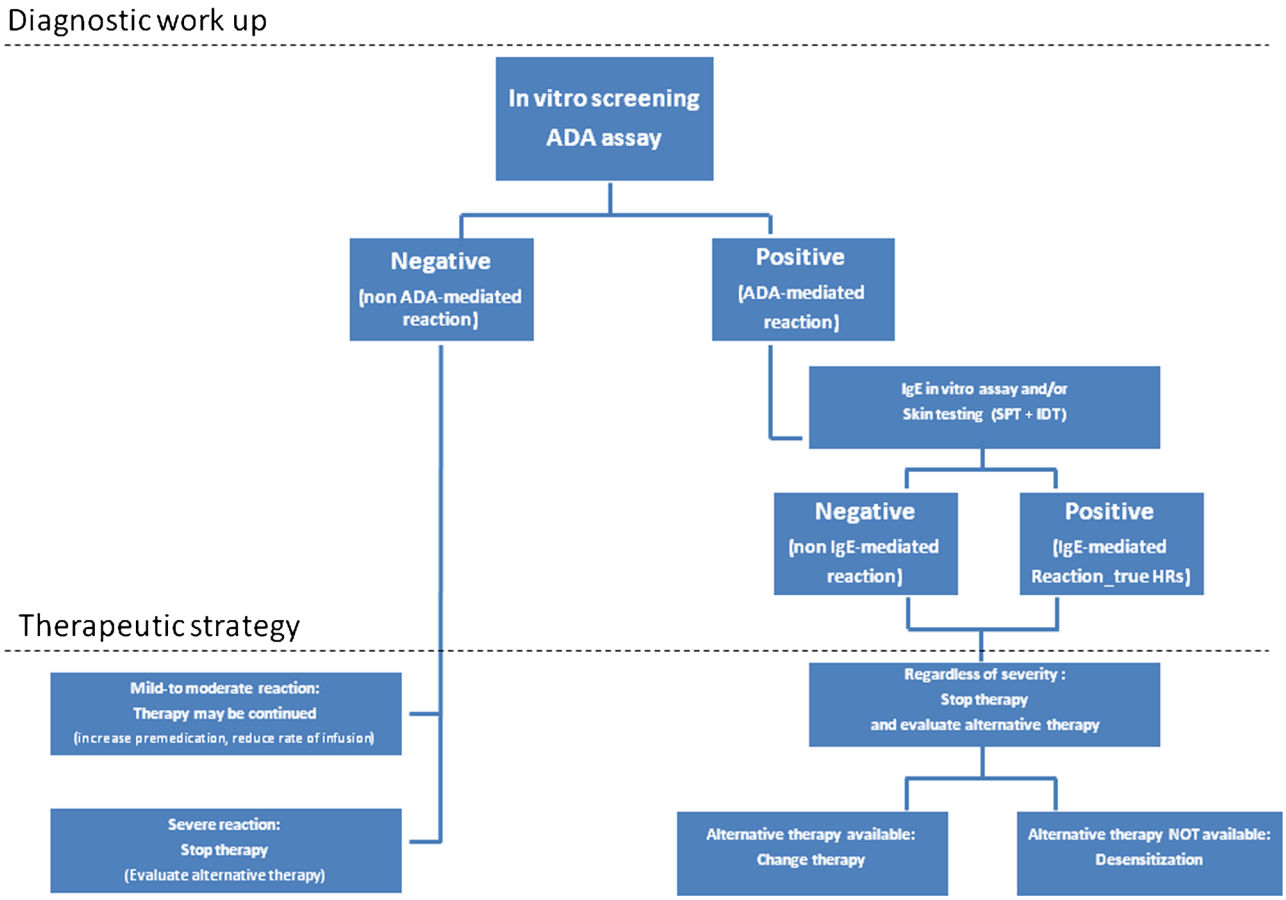

Fig. 2. General algorithm for allergological work-up of immediate hypersensitivity reactions to biological agents.

reactions are still poorly demonstrated. In fact, very few data are available that correlate ADA positivity with skin vasculitis during treatment with rituximab [51] or the occurrence of thromboembolic events during adalimumab treatment [41]. On the other hand, the association of the onset of a serum sickness syndrome that is a classic type III HRs sustained by the production of antibodies to foreign immunoglobulin with the formation of immune complexes, with the presence of serum ADA is lacking. Finally, no data are available about the role of T cell assay in the evaluation of delayed skin reactions.

In vivo tests

In vivo tests have been carried out mainly in patients who developed IFN-related generalized skin reactions. IDT at delayed reading (average of 72 h) seems to be useful in the management of generalized reactions to IFNs [52–54]. However, no conclusive results are available to define the role of in vivo tests. The role of the patch test, helpful in the diagnosis of delayed drug reactions, has never been defined in the diagnosis of delayed cutaneous reactions to BAs.

Compliance with Ethical Standards

Conflict of Interest

Dr. Alessandra Vultaggio declares that she have no conflict of interest.
Dr. Andrea Matucci declares that she have no conflict of interest.
Ms. Francesca Nencini declares that she have no conflict of interest.
Dr. Sara Pratesi declares that she have no conflict of interest.
Dr. Enrico Maggi declares that he have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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