

Position statement

Measurement of specific and nonspecific IgG₄ levels as diagnostic and prognostic tests for clinical allergy

AAAAI Board of Directors

A pathogenic role for IgE-dependent reactions in allergic diseases has been established. Evidence for IgE antibodies, however, is lacking in many cases of chronic asthma, rhinitis, and urticaria. Some investigators have also attributed to one of the subclasses of IgG, namely IgG₄, the activity of an effector or anaphylactic antibody.

IgG₄ AS AN ANAPHYLACTIC ANTIBODY

A 1973 study¹ demonstrated that in baboons, human IgG₄ blocked 24-hour passive cutaneous anaphylaxis mediated by IgE antibodies from pollen-sensitive patients. Stanworth² postulated that this blocking effect was the result of binding to specific mast cell Fc receptors for IgG₄ on primate mast cells, which in turn interfered with the binding to nearby closely associated IgE Fc receptors of specific IgE antibodies, presumably by a type of steric hindrance mechanism.² It was also presumed that the human IgG fraction used by Parish³ in an earlier study to confer passive cutaneous anaphylaxis on monkey skin for 1 to 4 hours was most likely IgG₄.

Citing these studies as a basis, Gwynn et al.⁴ reported that they had induced delayed asthma in response to inhaled allergens in patients who had negative RAST results for IgE antibodies but positive RAST results for IgG₄ antibodies to these allergens. These authors concluded that IgG₄ antibodies play an immunopathogenic role in severe asthma, and possibly other allergic diseases such as eczema, on the basis of their finding of high specific and nonspecific IgG₄ levels in the sera of their patients. Others were unable to confirm those findings.⁵

In an effort to link IgG₄ with clinical allergy through a mechanism similar to IgE-mediated de-

granulation of mast cells and basophils, investigators have concluded that IgG₄ acts as an anaphylactic antibody, especially for food,⁶ pig,⁷ and midge⁸ antigens. These conclusions, however, have been seriously questioned by nonconfirmatory studies.^{9, 10}

IgG₄ AS A PROTECTIVE ANTIBODY

Limited success in confirming IgG₄ as an effector antibody in clinical situations directed attention to its role as a protective factor. Immunotherapy is associated with the production of blocking antibodies, so named because of their ability to block the Prausnitz-Küstner reaction for reaginic antibodies in human beings. Evidence that such blocking properties reside in the IgG₄ fraction is based on findings of increases in specific antiallergen antibodies of this subclass in patients receiving immunotherapy for insect venom and house dust mite hypersensitivity.¹¹⁻¹³

Despite the preliminary nature of many of these studies, which were specifically directed toward two main groups of allergens, commercial interests have promoted the clinical efficacy of the measurement of serum IgG₄ levels, both specific and nonspecific, for the diagnosis and prognosis of a variety of allergic diseases unrelated to venom or house dust mite hypersensitivity.

As an explanation for the paradoxical situation of the same antibody acting in a pathogenic and a protective capacity, Stanworth¹⁴ cited evidence of heterogeneity of IgG₄ antibodies. He postulated that the majority of IgG₄ myeloma proteins, which he found were unable to bind to human mast cells, represent protective antibodies and the 25% that do seem to bind were effector types.

CONTRADICTION STUDIES OF THE BLOCKING ANTIBODY ROLE

Later studies, in which more specific monoclonal antibody reagents were used for assays of all IgG subclasses including IgG₄, demonstrated that most IgG subclasses increased during immunothera-

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py.^{15, 16} It was also determined that total serum IgG₄ levels are low in infants and children under the age of 3 years and rise with age in subjects both with and without allergic diseases.¹⁰ Normal levels for total serum IgG₄ are not yet well established.

In summary, a definitive role for IgG₄ as either an anaphylactic or a blocking antibody, or both, is not supported by the following information.

1. The short-term sensitizing antibody described by Parish,³ which served as a precursor to the concept of a non-IgE anaphylactic antibody, has not been conclusively identified as belonging to any IgG subclass.¹⁷
2. Receptors for IgG₄ on human basophils and mast cells have not been established.¹⁸
3. It has not been determined that bronchial or other direct challenges can reproduce clinical disease solely in the presence of specific IgG₄ antibodies to the antigen challenge.¹⁹
4. Specific and total IgG₄ serum levels do not always rise in the patient who has clinical improvement during immunotherapy, and therefore this test cannot be used as a marker for treatment efficacy.²⁰
5. IgG subclasses other than IgG₄ rise in response to long-term exposure to allergens in persons with both symptomatic and asymptomatic conditions.^{15, 16, 21-25} These allergens include birch pollen, *Cladosporium* species, yellow jacket venom, timothy grass, imported fire ant, mite (*Der p* I), ryegrass (*Lol p* I), β -lactoglobulin from cow's milk, and hen ovalbumin.

Recent studies suggest a possible role for antigen-specific IgG₄ measurements in two categories: food intolerance and immunotherapy against bee venom sensitivity. Higher concentrations of α -casein IgG₄ antibodies (>9.98 μ g/ml) appeared to correlate with milk-induced eczema in adults.⁶ However, results of this unblinded study have not been confirmed.

In 10 patients who successfully tolerated bee stings up to 2 years after cessation of a course of venom immunotherapy, bee venom phospholipase A₂-IgG₄ antibodies remained elevated.¹¹ This finding suggests a causal relation of specific IgG₄ and clinical protection from bee stings. However, others using a different assay in 46 patients, found that anti-bee venom IgG₄ levels gradually waned after 4 years of immunotherapy, whereas clinical protection appeared to remain.²⁶ They concluded that long-term immunity and short-term protection were mediated by different mechanisms.

Additional suggestions for antigen-specific IgG₄

measurements would be to monitor an immunologic, though not necessarily a clinical, response to allergen immunotherapy and to confirm an exposure and immunologic response to an occupational agent.²⁵ However, these suggestions are hypothetical, and their practicality has not been studied.

POSITION STATEMENT—1994

The initial enthusiasm by some for the measurement of total and specific IgG₄ as diagnostic and prognostic tools for allergic diseases has been tempered in the light of recently published studies. Studies that use improved reagents and assays and measure other IgG subclasses have cast doubt that IgG₄ has either an exclusive role as a protective antibody or a major alternative role to IgE as an anaphylactic antibody. Well-designed studies should continue to be performed in order to more conclusively delineate the biologic significance of IgG₄. However, in view of the incomplete and conflicting data presently available, the American Academy of Allergy and Immunology recommends that the measurement of IgG₄ should not be part of the diagnosis and treatment of patients with allergic diseases.

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