Orchestration of immunoglobulin isotypes, subclasses, and specificities in patients receiving intravenous IgG or subcutaneous immunotherapy and those with chronic rhinosinusitis with nasal polyps: Toward precision medicine

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A common principle is illustrated in several different approaches to treating inflammatory disease reported in 3 recent articles published in the Journal: (1) intravenous IgG (IVIG) treatment in patients with autoimmune disease, (2) subcutaneous immunotherapy (SCIT) in patients with grass pollen–induced allergic rhinitis, and (3) anti-IgE injections in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) targeting IgE. In each of these studies, IgE is the immediate cause of the inflammation, irrespective of whether it acts as an antibody or an antigen, and the therapy depends on the ability of IgG to interfere with the activity of the IgE. This review briefly summarizes the evidence in these articles for the interplay between the different isotypes and clinical relevance.

IVIG: THE PART OF ANTIBODY ISOTYPE AND POSTTRANSCRIPTIONAL MODIFICATION

IVIG is widely used for suppression of autoantibody-triggered inflammation, but the mechanism of action has been elusive. A minor fraction of IgGs containing sialylated Fc regions is responsible for the anti-inflammatory action of IVIG, implicating the IgG antibody isotype and glycosylation state in the mechanism of action. Further work in a murine model of arthritis revealed that secretion of IL-33 on sialylated Fc binding to CD209+ myeloid cells led to expansion and activation of basophils, secretion of IL-4, and, in turn, upregulation of inhibitory FcγRIIB on macrophages. The effect was recapitulated by intermediates in the pathway, either IL-33 or IL-4. IVIG Fcγ retained the activity of IVIG.

SCIT: THE PART OF IgG SUBCLASS

SCIT in patients with grass pollen–induced allergic rhinitis involves a long course of subcutaneous injection of a grass pollen allergen extract with dose escalation until IgG4 concentrations in serum reach a plateau, after which the final dose is maintained until the end of the course. The design was informed by the observation that IgG4, initially an IgG subclass of relatively low abundance in serum (<1 mg/mL vs >10 mg/mL for IgG1) increases 10- to 100-fold in concentration, reaching a plateau at approximately 6 months. IgG4 is associated with the successful outcome of SCIT.

Recent work by Galeotti et al has uncovered a simpler mechanism. It is well established that IL-3 upregulates the high-affinity IgE receptor FceRI on mast cells and basophils, thereby priming the cells for IgE-mediated allergen activation. Galeotti et al isolated basophils from healthy human donors and showed that the priming activity of IL-3 greatly exceeds that of IL-33. Preincubation of the basophils with IL-3 enhanced the IVIG-induced expression of the early basophil activation marker CD69 and induced secretion of IL-4, IL-6, and IL-8 without causing degranulation. The limited effect was attributed to the lack of significant CD69 expression.

Antigen specificity was confirmed by the activity of the F(ab')2 fraction by contrast to the previously proposed Fcγ. The in vivo relevance of the anti-IgE was supported by the observation of CD69+ basophils in the circulation of patients with inflammatory myopathies. These results confirmed previous findings that human serum contains IgG antibodies specific for IgE; the antibodies either enhanced or blocked the activity of IgE, depending on the donor.

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allergen-specific IgE and IgG4 levels in nasal fluid rather than sera as the biomarker. This resulted in an improved correlation with clinical outcome \((r = 0.6\) for nasal fluid as opposed to \(r = 0.5\) for sera). They also found the blocking mechanisms to be identical and the efficacy to be related to levels of allergen-specific IgE in fluid. Depletion of total IgG from nasal secretions, as from serum, led to an increase in facilitated antigen binding. Reconstitution of removed IgG with the IgG minus fraction would further strengthen their conclusion, and depletion of the individual subclasses would add precision. Use of the nasal fluid, evidently secreted from the adjacent nasal tissue, as for IgE, and representing the source of the antibodies, is the key to success. In a previous study IgG4 was found to be the predominant subclass to undergo local switching to IgE; this would be consistent with the accumulation of advantageous mutations accompanying multiple switching events in the immunoglobulin heavy-chain locus in B-cell precursors, resulting in affinity maturation (Fig 1).

**CRSwNP: THE PART OF ISOTYPE AND CLONOTYPE**

It is well established that local IgE antibodies in nasal polyp tissue are functionally active and capable of eliciting mast cell activation in an antigen-specific manner. Shamji et al demonstrated that this activity might be regulated by competition between IgG and IgE antibodies of the same specificity. They preformed mixture of a grass pollen extract or *Staphylococcus aureus* enterotoxin B with homogenates from the nasal polyps of patients with CRSwNP containing IgE antibodies specific for the respective antigens provoked T-cell proliferation and basophil activation with histamine release. These proinflammatory activities increased on depletion of IgG from the homogenates and decreased on mixing the 2 fractions together, proving that antigen-specific IgG competes with IgE of the same specificity. It has long been assumed that the antagonism between IgG and IgE in such processes results from shared clonality between the IgG and IgE. As proof of principle, most IgEs in allergic patients result from sequential heavy-chain switching of IgG-expressing memory B cells to IgE. Thus the switched IgE\(^+\) B cells inherit the specificity of their IgG precursors, which earlier underwent somatic hypermutation and affinity maturation in the immune response (Fig 1).

In line with a recent study of local antibody repertoires in patients with allergic rhinitis, Shamji et al report extensive sharing of clonal signatures between IgG and IgE repertoires, although this has not yet been nailed down to the actual specificities. The results nevertheless suggest the potential capacity of the IgG to compete with IgE for antigen. Although coexpression of the 2 antibodies would suppress inflammation, later switching to IgE might lead to development or aggravation of CRSwNP. Shamji et al propose that recombinant antigen-specific IgG antibodies derived from identified allergen-specific IgE V-region sequences could be used in the passive immunization of patients exposed to potentially dangerous antigens. Experiments with recombinant antibodies against *S aureus* enterotoxins have demonstrated proof of principle.

**SYNTHESIS**

Current approaches to treating patients with autoimmune diseases, grass pollen–induced allergic rhinitis, and CRSwNP serve their purpose but lack precision. A minute fraction of IVIG, the anti-IgE fraction, is relevant to autoimmunity. IgGs that can switch to grass pollen–specific IgEs on exposure to grass are diverse in terms of their antigen epitopes and variety, but the dominant allergens and epitopes can be determined and used for SCIT. Anti-IgE remains a possible effective treatment for CRSwNP, pending identification of the pathogenic IgEs and their activities. Further research on the interplay between isotypes, subclasses, and clonotypes might direct the development of more precisely targeted therapies.

**REFERENCES**

