Correspondence

Reply

To the Editor:

I thank Giorgio Ciprandi[1] for commenting on my recent article[2] and for proposing, on the basis of results of reports cited in his letter, that serum levels of allergen-specific IgE (sIgE) could be considered a potential biomarker to identify those patients with allergic rhinitis most likely to respond to allergen-specific immunotherapy (SIT). Specifically, Ciprandi highlighted articles reporting that subjects with allergic rhinitis whose blood sIgE level exceeded specified amounts were much more likely to respond to SIT than those with lower levels of sIgE; he also cited 1 article reporting conflicting results.

However, Ciprandi also has pointed out certain limitations of these studies. For example, in the study by Di Lorenzo et al,[3] of 279 patients with allergic rhinitis who were determined to be monosensitized to grass, *Parietaria judaica*, *Olea europea*, or house dust mites (HDMs), a serum sIgE/total-IgE ratio of more than 16.2 predicted a favorable clinical response to SIT with a sensitivity of 97.2% and a specificity of 88.1% (vs corresponding values of 87.6% and 57.5% for sIgE alone, using a decision point of 9.5 kAU/L). In addition to focusing solely on monosensitized subjects, the authors of that study acknowledged that it lacked a placebo group and was retrospective, and that their findings should be followed up with a double-blinded study.

As noted by Ciprandi, the study by Fujimura et al,[4] which was a randomized, double-blind, placebo-controlled study of sublingual immunotherapy (SLIT) in subjects with Japanese cedar pollinosis, suggested that SLIT was more effective in patients with low than high sIgE/total-IgE ratios. However, in that study, intention-to-treat analyses revealed no significant difference in the symptom medication score in the SLIT group versus the placebo group, whereas in the 88 subjects who were on treatment, the symptom medication score was significantly improved versus the placebo group in the second (but not the first) pollen season analyzed. Of course, in addition to the issue raised by Ciprandi—the rather limited clinical efficacy of SLIT observed in the Fujimura et al[4] study—the possibility must be considered that the discordant results regarding the predictive value of sIgE/total-IgE ratios in that study and the study conducted by Di Lorenzo et al[3] also might have been influenced by other differences among the studies, including in the allergens analyzed and in the genetic and environmental factors in the assessed patient populations.

The results obtained in the other studies mentioned by Ciprandi also would need to be confirmed in larger, well-designed prospective studies. For example, in their study of SLIT using a single allergen extract in 62 subjects (86.7% of them reported to be polysensitized), Ciprandi et al[5] found that 84% of the patients met the authors' definition of responders (based on their clinical improvement and medication use) and that a receiver-operating curve analysis determined that an sIgE concentration of 14.3 kU/L in the blood was optimal for discriminating responders versus nonresponders, with an associated sensitivity and specificity of 92.5% and 73.1 %, respectively. The authors noted that their study should be followed up with trials in larger cohorts of patients. Similarly, Ciprandi and Silvestri[6] performed a retrospective analysis of a group of 174 consecutive patients with allergic rhinitis, asthma, or both (exclusion criteria included atopic dermatitis and allergies to multiple allergens) who were treated for at least 3 years with SLIT, and defined a responder as an individual with an improvement in visual analogue scale (VAS) score—assessing both clinical improvement and medication use—of at least 30% compared with the pretreatment baseline score. In that study, a blood sIgE level of more than 9.74 kU_A/L discriminated responders versus nonresponders with a sensitivity and specificity of 96.5 and 100.0%, respectively. However, as noted by the authors, their study "was retrospective and not adequately controlled, it should be followed up by rigorous prospective trials in larger cohorts to confirm the findings." A subsequent open retrospective analysis was performed by Tosca et al,[7] who studied 39 HDM-allergic children with allergic rhinitis, asthma, or both who had been treated for 3 years with SLIT for HDM, using the children's perception (in a VAS) of improvement in allergic symptoms and reduction in medication use as the end point. In that study, using serum sIgE of 10 kU/L or more as the cutoff, a response to SLIT was observed in 94.7% of the subjects with a high sIgE versus 13% of those with a low sIgE. However, as noted by the authors, the way responders were defined in that study using a particular VAS score "was arbitrary and not validated."

One way of summarizing the results of the studies cited in Ciprandi's letter would be to conclude that although it may be possible to identify a particular cutoff value of serum sIgE (or for the sIgE/total-IgE ratio) that can predict the likelihood of responsiveness to SIT in certain defined groups of subjects diagnosed with allergic rhinitis, one cannot be sure without additional studies that the same results would be obtained in well-designed prospective studies of other patient populations.

Another consideration is that findings regarding the utility of sIgE cutoff points that are determined for patients with one type of allergic disorder (eg, allergic rhinitis) may not be applicable to other settings. For example, van Erp et al[8] concluded in their review that while "sensitization to Ara h 2 is the best predictor for clinically relevant peanut allergy in children and adults" …. "It is, however, important to remark that cutoff points of sIgE to Ara h 2 that predict tolerance or allergy vary between different study populations, different age groups and geographical regions, and validation studies performed in different settings are necessary to implement cut-offs in daily practice."

Moreover, attempts to define predictive biomarkers for responsiveness to SIT also should take into account the possibility that some individuals may experience amelioration of their disorder even without specific therapeutic intervention, and that this outcome also might be predictable on the basis of proper choice of biomarkers. For example, in a population-based study of the natural history of peanut allergy and possible predictors of its resolution in the first 4 years of life, Peters et al[9] used oral food challenges to test for clinical reactivity to peanut, and also performed skin prick tests (SPTs) and sIgE measurements, to obtain what they reported to be the first such data set in which all participants underwent oral food challenges at both diagnosis and follow-up, irrespective of SPT and sIgE results. They found that peanut allergy resolved without treatment in 22% (95% CI, 14% to 31%) of these children by age 4 years and that thresholds for SPT responses and sIgE levels at age 1 year that had a 95% positive predictive value for persistent peanut allergy were an

SPT-induced response of 13 mm or greater and an sIgE level of 5.0 kU/L or greater. Notably, Peters et al[9] also found that sIgE levels to Ara h 2 at 1 year were not able to predict persistent peanut allergy, despite the group's previous finding that levels of sIgE to Ara h 2 were highly accurate in the diagnosis of peanut allergy.[10]

Finally, advances in technology for assessing potential biomarkers, and in computational methods, are permitting the modeling and testing of diagnostic or predictive algorithms that incorporate the results of both multiple different tests and the clinical features of disease. Properly designed and analyzed large prospective studies using such approaches would allow testing the value of measuring levels of *single* analytes, such as blood sIgE, to test directly whether they have utility as simple, relatively inexpensive, and easily performed predictive biomarkers of clinical responsiveness to SIT, at least in the well-defined clinical populations examined. Such trials also would allow one to test the potential utility of simultaneously measuring large sets of biomarkers as part of efforts to monitor the severity of disease and/or the efficacy and durability of SIT or other types of treatment in individual subjects. In principle, succeeding in identifying such robust biomarkers of responses to SIT (whether as single or multiple analytes) would permit one to discontinue SIT or move to a different form of SIT or other types of treatment in those subjects in whom SIT is not working, as well as to reassure those patients who are achieving and sustaining a favorable response to treatment. There are many *candidate* biomarkers to consider testing, in addition to sIgE, in the development of such "disease and therapy monitoring approaches." Although a thorough review of that topic is beyond the scope of this letter, such candidate biomarkers include measurements of levels and immunological function of sIgGs (such as $sIgG_4$[11]), ratios of activating (eg, sIgE) and inhibiting (eg, $sIgG_4$) antibodies (and their ability to influence responsiveness of blood basophils to allergen challenge),[12] and changes in the numbers and phenotypes of various T-cell populations that have been implicated in allergic disorders.[13] However, much additional work, and time, will be needed to determine the extent to which such approaches can move from the domain of research into standard clinical practice to help us to improve our ability to predict, diagnose, and monitor allergic diseases, and to individually tailor the treatment of patients with allergic disorders.

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