TABLE I. Discordance rate between SPT responses to pollen extracts and serum IgE levels to their major allergenic molecules

	SPT, >3 mm, no.	SPT, positive clinically relevant fraction, no.	Relevant SPT response positivity not confirmed by IgE to major allergenic proteins, no. (%)			*P* value*
			<0.70 kU/L	<0.35 kU/L	>0.35 and <0.70 kU/L	
Grass	592	568	56 (9.5)	38 (6.4)	18 (3.2)	.053
Olive	405	390	111 (27.4)	69 (17.0)	42 (10.8)	<.001
Pellitory	259	257	78 (30.1)	77 (29.7)	1 (0.4)	.924
Cypress	287	184	28 (9.8)	22 (7.7)	6 (3.3)	.374
Betulaceae	309	252	146 (47.2)	135 (43.7)	11 (4.4)	.374
Mugwort	163	65	45 (27.6)	42 (25.8)	3 (4.6)	.707

*The χ^2 test was used to compare frequencies (<0.70 vs <0.35 kU/L).

sure that the individual patient's IgE is not merely recognizing profilins or polcalcins in that pollen extract but that he or she is truly reacting against the major allergenic molecules.

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Knowledge of the literature is crucial for meta-analyses

To the Editor:

We read with interest the recent meta-analysis by Dretzke et al[1] indirectly comparing subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for seasonal allergic rhinitis. In 2012, this very journal published the first meta-analysis–based indirect comparison of SCIT and SLIT for seasonal allergic rhinitis.[2] In that meta-analysis, which the authors did not mention, only randomized controlled trials on grass allergens were included, whereas Dretzke et al[1] also included other airborne allergens. However, even though the study by Dretzke et al was published 1 year later, it offers no new information for grass, and 5 relevant studies on SCIT, Bousquet et al,[3] Dolz et al[4] (for symptom score [SS]),[4] DuBuske et al,[5] Pfaar et al,[6] and Pastorello et al[7] (citing only those regarding grass allergens), were not included. The study by DuBuske et al[5] could have been included because the data concerning SSs and medication scores, which were not available in the original study, were published in the earlier meta-analysis,[2] which was obtained from the authors. The study by Pfaar et al[6] reported both SSs and medication scores. In the study by Dolz et al,[4] nasal and conjunctivitis SSs, which were reported separately, were very similar, and therefore no difference in the overall result appears if only nasal SSs are included. For similar reasons, the studies by Bousquet et al[3] and Pastorello et al[7] were also included in the earlier analysis to avoid a loss of data. Considering these studies, even the controversial study by DuBuske et al,[5] the only non-European study, the difference in efficacy between SCIT and SLIT, at least for grass, was more evident (SS-SMD [standardized mean difference] = −0.92 [or −1.05 with exclusion of the study by DuBuske et al[5]] for SCIT vs −0.35 for SLIT). This difference is sufficiently large to suggest the superiority of SCIT over SLIT for grass, even considering (1) the high heterogeneity, which was discussed in detail in the earlier meta-analysis and in the subsequent correspondence,[8] and (2) the lower SCIT efficacy over time described by Dretzke et al[1] but less evident for European grass studies. However, this difference in

efficacy over time is not sufficient to doubt the validity of the older studies. In particular, the treatment duration seems to be correlated with the efficacy of SCIT: studies with longer treatment (≥1 year) appear more effective than studies with shorter treatment (<1 year).[2] It is worth pointing out that the most recent studies commonly used an ultrashort protocol for SCIT administration, aiming to provide more convenient treatment (to be more similar to SLIT) by reducing the number of injections, office visits, and so on, even though a 3-year course of therapy is generally recommended.

In their analysis of the relative efficacy of SCIT versus SLIT over time, Dretzke et al[1] conclude that the probability of SCIT being more effective shifts to SLIT being more effective in approximately 2007 by using the deviance information criterion (DIC), further reporting a very small difference between the 2 models. Much criticism can be found in the literature on the use of the DIC in a model-selection procedure and on the significance of the difference between the DICs of 2 competing models. For example, see the discussion by Moreno et al[9] presented at the Annual Meeting of the Royal Statistical Society in September 2013.

Another concern with the methodology used by Dretzke et al[1] regards the covariates they used. The covariate values for each study are reported neither in the published article nor in the supplementary material. This is particularly important, especially when a variable is categorized by the authors. For example, "year of publication" is divided into 3 categories, 2000, 2005, and 2010, without explaining why. But do these years represent the center of the classes or the cutoff points? In the first case, assuming a category of 2008-2011, they considered only 2 SCIT studies against 14 SLIT studies. Therefore this analysis was conducted comparing 2 very disproportionate groups, which raises concern about the reliability of the conclusions.

In conclusion, the widespread use of SLIT, particularly in southern European countries, does not appear justified on the basis of the available evidence, at least for grass, because its efficacy was never shown to be greater than or equal to that of SCIT, and in contrast to what is claimed, the number of adverse events, both those that are mild to moderate and those serious enough to cause the withdrawal of patients from randomized controlled trials, is higher than that of SCIT, except for the anaphylactic reactions, which occurred in a very small number of cases.[2] We do agree with Dretzke et al[1] that a direct comparison between SLIT and SCIT is needed for a confident judgment on this matter, as was mentioned in the earlier meta-analysis.[2]

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Facilitated dissociation of IgE versus cell replacement

To the Editor:

While exploring the ability of designed ankyrin repeat proteins (DARPins) to induce dissociation of IgE from FcεRI on basophils, Eggel et al[1] noted that omalizumab also facilitates dissociation of IgE from FcεRI. One of the interesting characteristics of treating patients with omalizumab is the rapid decrease in cell-surface expression of both IgE and FcεRI on peripheral blood basophils and a slow loss of the same molecules on tissue mast cells.[2-4]

Because our early studies found that 10 to 200 μg/mL of CGP51901 (an anti-IgE antibody from the former Tanox Corp, Houston, Tex; ie, concentrations that were 250- to 5000-fold greater than needed to trap dissociating IgE)[5] did not accelerate the very slow dissociation of IgE from basophils *in vitro*,[6] a different mechanism for the rapid decrease of IgE on basophils *in vivo* was proposed.[7] This mechanism was based on the rapid replacement of basophils in circulation with new cells that had not experienced IgE-dependent upregulation of FcεRI expression[7,8] and provided a mechanism to distinguish mast cells from basophils that was dependent on different rates of cell turnover. However, the ability of omalizumab to facilitate dissociation raises the possibility that a cell replacement mechanism is not necessary to explain rapid loss of expression.

Eggel et al[1] explored primarily very high concentrations (1-8 mg/mL) of omalizumab to observe the induced dissociation. In their discussion the authors suggested that omalizumab levels in patients treated with the antibody could exceed 1 mg/mL. However, pharmacokinetic studies of subcutaneous injection of omalizumab based on the published dosing table demonstrate a maximum concentration (Cmax) of between 10 and 50 μg/mL