Correspondence

Methodological aspects of a meta-analysis of grass pollen allergen sublingual immunotherapy tablets

To the Editor:

We have identified a number of issues affecting the conclusions of a recently published systematic review and meta-analysis of the efficacy of grass pollen allergen sublingual immunotherapy (SLIT) tablets for seasonal allergic rhinoconjunctivitis.[1] The validity of a meta-analysis depends on the quality of the systematic review on which it is based and, to a lesser extent, on the conclusions that the authors draw from it. Although Di Bona et al[1] applied a rigorous methodology to the meta-analysis *per se*, many aspects of their report, including their interpretation of the results, require clarification and comments acutely described in this article's Online Repository at www.jacionline.org.

The authors selected 13 randomized controlled trials for the symptom score (SS) and 12 for the medication score (MS). Their choice of 2 studies can be questioned, even though these 2 studies reportedly had little influence on the study's overall findings. They performed a sensitivity analysis that excluded 5 studies at high or moderate risk of bias, and results of this analysis produced similar results, suggesting trial quality only marginally affects outcomes.

The authors suggested that the clinical improvement with symptomatic medications is superior to that of grass pollen tablets, whereas Devillier et al[2] concluded that grass pollen SLIT had a greater clinical effect than symptomatic treatments (see Fig E1 in this article's Online Repository at www.jacionline.org), as confirmed by Matricardi et al,[3] providing evidence for subcutaneous immunotherapy (SCIT). An effect size based on the standardized mean difference (SMD; the number of SDs between means), or Hedges g value, is not the same as the "intervention effect" or "effect estimate" classically used in medicine.

The authors analyzed SSs and MSs separately as the primary outcomes for SLIT, whereas a score combining symptoms and rescue medication use is generally favored as the primary outcome by both regulatory agencies and professional societies.[4]

The authors suggested that a single-point change in the Rhinoconjunctivitis Total Symptom Score (RTSS) is not clinically relevant, whereas Devillier et al[5] recently concluded that "the MID in the RTSS was consistently estimated as 1.1-1.3."

The authors make some unusual comments concerning safety. When comparing the safety of SLIT with that of SCIT, Di Bona et al[1] write that "in contrast, the total number of adverse events is higher in SLIT than in SCIT." First, this statement is debatable, especially if the incidence of local reactions to SCIT is taken into account. They did not take account of the incidence, severity, duration, recurrence, and systemic versus local nature of the adverse events (AEs).

The authors do not consider the persistent efficacy conveyed by allergen immunotherapy (AIT)'s disease-modifying effect through induction of immune tolerance that can translate into long-term symptomatic improvement years beyond discontinuation.

This long-term benefit should be included in the patient/physician-shared decision-making discussion.

In conclusion, Di Bona et al[1] performed a rigorous meta-analysis but overinterpreted the results while losing sight of other important parameters.

Linda S. Cox, MD[a]
Alain Didier, MD, PhD[b]
Pascal Demoly, MD, PhD[c]
Ulrich Wahn, MD, PhD[d]
André Pradalier, MD[e]
Anthony J. Frew, MD[f]
Philippe Devillier, MD, PhD[g]

From [a]the College of Osteopathic Medicine, Nova Southeastern University, Davie, Fla; [b]the Respiratory Diseases Department, Rangueil-Larrey Hospital, Toulouse, France; [c]the Allergy Division, Pulmonology Department, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France, and Sorbonne Universités, UPMC Paris 06, UMR-S 1136 INSERM, IPLESP, Equipe EPAR, Paris, France; [d]the Department of Pediatric Pneumology and Immunology, Charité Virchow-Klinikum, Berlin, Germany; [e]retired, Paris, France; [f]the Department of Respiratory Medicine, Royal Sussex County Hospital, Brighton, United Kingdom; and [g]UPRES EA 220, Université de Versailles Saint-Quentin, Foch Hospital, Suresnes, France. E-mail: lindaswolfcox@msn.com.

Disclosure of potential conflict of interest: L. S. Cox has received personal fees from Greer. A. Didier is a board member for and has received lecture fees from Stallergenes and ALK-Abelló. P. Demoly has received consultancy fees from ALK-Abelló, Circassia, Stallergenes, Allergopharma, DBV, Thermo Fisher Scientific, Chiesi, and Pierre Fabre Médicament and has received lecture fees from Ménarini, MSD, and AstraZeneca. U. Wahn is a board member for and has received consultancy fees, research support, lecture fees, and travel support from Stallergenes. A. J. Frew has received consultancy fees from Stallergenes. P. Devillier has received consultancy fees, participation fees and payment for manuscript preparation from Stallergenes; is a board member for Meda Pharma; has received consultancy fees from Stallergenes, ALK-Abelló, and GlaxoSmithKline; has received lecture fees from Stallergenes and ALK-Abelló; and has received travel support from Stallergenes and Meda Pharma. A. Pradalier declares that he has no relevant conflicts of interest.

REFERENCES

1. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med 2015;175:1301-9.
2. Devillier P, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Med 2014;12:71.
3. Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. J Allergy Clin Immunol 2011;128:791-9.
4. Pfaar O, Demoly P, van Wijk RG, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis; an EAACI Position Paper. Allergy 2014;69:854-67.
5. Devillier P, Chassany O, Vicaut E, de Beaumont O, Robin B, Dreyfus JF, et al. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. Allergy 2014;69:1689-95.

http://dx.doi.org/10.1016/j.jaci.2016.01.039

METHODS

Studies chosen for meta-analysis

To perform their meta-analysis, Di Bona et al[E1] selected 13 randomized controlled trials (RCTs) for the SS and 12 for the MS. Their choice of 2 studies can be questioned. Despite the researchers' stated objective of assessing the "efficacy and safety of the grass pollen sublingual tablets licensed as drugs," 2 trials of an unlicensed formulation were included in their analysis, a 1999 publication featuring a 100-IR tablet[E2] and a 2004 publication featuring the maintenance administration of three 100-IR tablets 3 times a week (rather than the authorized once-daily administration).[E3] The 100-IR tablet administered in these 2 studies was not the same as the licensed 100-IR 5-grass tablet used for updosing before maintenance treatment.[E4] Di Bona et al[E1] acknowledge this when they write, "The remaining RCT used tablets containing 5-grass pollen allergen extracts administered at a lower concentration (100 IR/mL, approximately 8.5 μg of the group of 5 major allergens)." Even though these 2 studies reportedly had little influence on the study's overall findings, their inclusion and citation confuse matters, especially because the 100-IR 5-grass tablet was no more effective than placebo in a pivotal phase IIb dose-ranging RCT.[E5]

Additionally, Di Bona et al[E1] performed a sensitivity analysis that excluded 5 studies at high or moderate risk of bias, and results of this analysis produced similar results (SMD, −0.25; 95% CI, −0.34 to −0.15; $P < .001$), which suggests trial quality only marginally affects outcomes.

SMD and relative clinical impact

On the basis of the calculated SMDs, the authors suggest that the clinical improvement seen with symptomatic medications is superior to that of grass pollen tablets. Devillier et al[E6] recently calculated the relative clinical impact (RCI) for grass pollen SLIT tablets and 4 classes of pharmacotherapy. The RCI, which seems more appropriate, has been defined by the World Allergy Organization as follows:

$$(100\times(\text{Score}_{\text{Placebo}}-\text{Score}_{\text{Active}})/\text{Score}_{\text{Placebo}})$$

on the basis of posttreatment scores. It has been applied by Matricardi and colleagues as part of a meta-analysis of grass pollen SCIT and pharmacotherapy.[E7,E8] In the study by Devillier et al,[E6] the weighted mean RCIs were −29.6% (range, −23% to −37%) for the 5-grass-pollen tablet, −23.5% (range, −7% to −54%) for nasal corticosteroids, −17.1% (range, −15% to −20%) for MP29-02, −15.0% (range, −3% to −26%) for H_1-antihistamines, and −6.5% (range, −3% to −10%) for montelukast (Fig E1). Devillier et al[E6] concluded that "grass pollen SLIT tablets had a greater mean RCI than H1-antihistamines and montelukast and much the same mean RCI as nasal corticosteroids." These findings were in line with the results of Matricardi et al,[E8] which also provide evidence that SCIT is at least as potent as pharmacotherapy in controlling seasonal allergic rhinitis/rhinoconjunctivitis (SAR) symptoms.

In an attempt to more precisely assess the benefit of AIT in patients with SAR, Howarth et al[E9] performed a *post hoc* analysis of 3 double-blind, placebo-controlled studies with the 5-grass-pollen tablet. Study centers were divided according to the mean level of symptom severity observed in each center's placebo-treated patients into low, middle, and high tertiles.[E10] They found the greatest improvement was always observed in the high-tertile centers, whereas a moderate decrease in the middle-tertile centers and almost no difference in the low-tertile centers were observed. These findings suggest that the magnitude of the effect depends on the severity of the allergic symptoms.

Furthermore, for the 5-grass-pollen tablet, a similar association between the magnitude of symptom improvement and symptom severity was found in the analysis by Devillier et al[E6] of four 5-grass pollen tablet studies, in which the weighted mean RCI of the high tertile's Average Adjusted Symptom Score (AAdSS) was −37.1% (range, −26% to −45%).

In 2011, Durham et al[E11] came to a similar conclusion (ie, the more severe the symptoms, the greater SLIT's clinical effect) when analyzing "days with severe symptoms" in a multicenter RCT trial of the timothy pollen tablet. They further demonstrated that the relative treatment effect of the timothy pollen tablets on the rhinoconjunctivitis combined score during the 5 seasons covered by the trial was strongly correlated with the cumulative pollen exposure in the beginning of the season, reaching about 33% for the highest pollen count.[E12]

Di Bona et al[E1] also cast doubt on the calculation by Cox et al[E13] of an RCI of 22% for the 5-grass-pollen tablet. However, the authors make a fundamental error by considering that a single retrospective rating (subject to recall bias) of the RTSS in the previous pollen season (14.90 in the study by Cox et al[E13]) is a measure of the peak severity score that would have been recorded in the absence of SLIT in the trial season. They go on to suggest that the true active versus placebo difference can be calculated by comparing 11.69 (14.9 minus 3.21, the calculated mean score over the study season) in the active group with 10.74 (14.9 minus 4.16) in the placebo group. An effect size based on the SMD (the number of SDs between means), or Hedges g value, is not the same as the "intervention effect" or "effect estimate" classically used in medicine.

Di Bona et al[E1] appear to have forgotten one of the key differences between clinical trials of symptomatic medications and clinical trials of SCIT or SLIT. The 7- or 14-day trials of symptomatic medications are typically performed during the peak pollen season in patients who are highly symptomatic at study entry. In contrast, treatment in a SLIT trial is initiated before the start of the expected pollen season, when patients are asymptomatic. One can never be sure that the randomized patients will actually be symptomatic during the coming study; this depends on many confounding factors. However, use of a retrospective estimate of a different parameter from the previous year is not the solution. In addition, the European Medicines Agency stated that only patients who experience an appropriate minimum level of symptoms before randomization during their relevant period of complaints should be enrolled. Retrospective scoring of symptoms can be used for this issue but suffers from memory bias and therefore should not be used further in the comparisons or analyses. Furthermore, Di Bona et al[E1] state that "SCIT has proven efficacy in treating allergic rhinitis" but do not apply their criticism of the RCI to SCIT trials (calculated by Matricardi et al[E8] in the same way as Cox et al[E13]).

Choice of scores used for meta-analysis

One can question the appropriateness of analyzing SSs and MSs separately as the primary outcomes for SLIT. A score combining both SSs and MSs is generally favored as the primary outcome by both European and American regulatory agencies and professional societies, such as the European Academy of Allergy and Clinical Immunology.[E4,E14-E16] World Allergy Organization taskforce recommendations on the methodological aspects of immunotherapy clinical trials recommend that a combined symptom and MS should be used as the primary outcome measure.[E17] Similarly, the European Academy of Allergy and Clinical Immunology Immunotherapy Interest Group recommended the use of a homogenous combined SSs and MSs as a standardized method to balance both symptoms and the need for antiallergic medication in an equally weighted manner.[E15] Such a standardized combined score can provide a simple analysis of the daily burden of disease.[E15] Combining SSs and SSs with equal importance is also associated with a large effect size, which is powered to demonstrate treatment efficacy.[E15]

Clinical relevance of a single-point change in the RTSS

When criticizing the efficacy of grass pollen tablets, Di Bona et al[E1] suggest that a single-point change in the RTSS is not clinically relevant. In contrast, Devillier et al[E18] recently studied the minimally important difference (MID) in the RTSS in patients with grass pollen–induced SAR and concluded that "the MID in the RTSS was consistently estimated as 1.1-1.3."[E18]

Observations on safety in an analysis of efficacy

First, the stated objective of this meta-analysis was to provide updated evidence on the effect of SLIT grass pollen tablets and not to perform a precise meta-analysis on safety. Di Bona et al[E1] make some unusual comments and wrong allegations concerning safety. They state that the "FDA requires that

Download English Version:

https://daneshyari.com/en/article/6062327

Download Persian Version:

https://daneshyari.com/article/6062327

Daneshyari.com