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Editorial OMICS International

The Evidence Based Efficacy of Sublingual Immunotherapy for Allergic Rhinitis, which is the Most Appropriate Estimate?

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Editorial

Meta-analysis was introduced to increase the statistical reliability of a treatment when only studies including a small number of patients were available. Concerning sublingual immunotherapy (SLIT), meta-analysis was of pivotal importance in demonstrating its efficacy and thus defining SLIT as a true option to conventional, injective immunotherapy. However, in recent years the development of pharmaceutical quality SLIT products, and the consequent need to fulfill the requirements of regulatory Agencies, resulted in a number of trials including a large number of patients (this defining them as "big trials"), that make superfluous and inappropriate to perform meta-analyses.

Sublingual immunotherapy (SLIT) is acknowledged as an effective treatment of allergic rhinitis (AR), that is achieved by its capacity to work on the causes of allergy and to modify the natural history of the disease [1,2]. Clinically, the first evidence was apparent with the systematic review and meta-analysis by Wilson et al. [3] that was followed by a number of other meta-analyses, as globally evaluated by Compalati et al. [4]. Meta-analyses were essential because most trials investigating the efficacy of SLIT included small populations of patients and this prevents a statistical robustness able to provide reliable observations. Instead, a meta-analysis combines the results of multiple studies to increase the statistical power and improves the estimate of the size of the treatment effect, as assessed by the main parameter of the standardized mean difference (SMD) of the included studies results [5]. AR induced by grass pollen has high prevalence the worldwide; therefore, the efficacy of SLIT on such allergy is of particular importance. As shown by meta-analyses, the clinical benefit with SLIT is, as previously observed with subcutaneous immunotherapy, dose-dependent. In fact, the efficacy was clearly higher in subjects receiving a monthly dose from 275 to 600 mcg compared with subjects receiving less than 275 mcg [6].

Indeed, the need to fulfill the requirements of the European Medicine Agency (EMA) for optimal quality of grass pollen tablets was met by the performance of the so called "big trials" including large number of patients [7,8]. In particular, the trial with the Phleum pratense tablet included 855 participants [7] and the trial with the 5-grass pollen tablet included 628 participants [8]. In addition, both products demonstrated persistent efficacy in long-term studies [9,10]. The approval by EMA of these standardized, pharmaceutical quality products was followed by their acceptation by the regulatory agencies in Canada, USA and Italy, where the Agenzia Italiana del Farmaco (AIFA) supported the full-reimbursement for the grass tablets in patients with grass pollen-induced AR [11].

Surprisingly, in front of such full evidence, further recent meta-analyses on SLIT for grass-pollen AR including the big trials questioned its efficacy [12]. Actually, flaws are often present in such meta-analyses including incorrect selection of trials, inappropriate use of evaluation parameters for the analysis, and incongruous analyses. In fact, meta-analysis does not fit with any application. For example, it was demonstrated that a meta-analysis of several small studies does not predict the results of a single large study that stays as gold standard to assess the efficacy and safety of a treatment. Actually, positive and negative predictive value of the meta-analyses was lower than 70% and the difference in point estimates between the randomized trials and the meta-analyses was statistically significant for only 5 of 40 comparisons [13,14]. The misuse of meta-analyses for SLIT was already noted by Milgrom [15] and a falling scientific interest for meta-analysis on SLIT emerged from the number of citations that strongly decreased in the latest years [12].

This lesson should be learned in view of the recent big trials on the house dust mite tablets for SLIT conducted in Europe [16,17], USA [18], and Japan [19], whose efficacy data do not need meta-analysis to confirm for mite allergy that same outcome achieved for grass pollen allergy, when new generation, pharmaceutical quality product for immunotherapy are used.

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