

2020 Updated Asthma Guidelines: Allergen immunotherapy



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In 2014, the National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group selected 6 priority topic areas to update the 2007 Expert Panel Report-3: Guidelines for the Diagnosis and Management of Asthma (EPR-3).¹ EPR-3 had recommended consideration of subcutaneous allergen immunotherapy (SCIT) in steps 2 to 4 for children ages 5 years and above, adolescents, and adults who have persistent allergic asthma. However, by 2014, sublingual allergen immunotherapy (SLIT) had become a common practice in many countries, and SLIT tablets were approved or under study in the United States; therefore, a review of the efficacy and safety of SCIT and SLIT was included as 1 of the 6 topics for review. As a background for consideration of these topic areas, systematic reviews were conducted on each. That on allergen immunotherapy (AIT) reviewed articles through May 8, 2017, and was released in March 2018 as Comparative Effectiveness Review Number 196: The Role of Immunotherapy in the Treatment of Asthma.² Appropriate new publications on the subject through October 2018 were also reviewed. The Expert Panel then reviewed the evidence, using the Grading of Recommendations Assessment, Development, and Evaluation approach. The Expert Panel deemed the following outcomes to be critical in making its recommendations: asthma exacerbations, asthma control, and asthma quality of life.³ It is questionable whether exacerbations and improved quality of life are critical outcomes to assess the efficacy of AIT. Participants in AIT trials are typically not those with frequent exacerbations or uncontrolled asthma; therefore, one would not look for significant improvement in these parameters. However, there is no mention of considering the persisting benefit following a course of AIT due to modification of the underlying disease.

The section³ begins by defining “allergic asthma” as asthma that becomes symptomatic after acute exposure to something to which the individual is allergic (eg, a pet) or during a specific season. Unfortunately, this does not include one of the most important causes of allergic asthma, the house-dust mite.

The Expert Panel recommendations follow; they were first released for public comment in December 2019 and in their final

form in this document.³ “In individuals ages 5 years and older with mild to moderate allergic asthma, the Expert Panel conditionally (moderate certainty of evidence) recommends the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in those individuals whose asthma is controlled.” However, “In individuals with persistent allergic asthma, the Expert Panel conditionally (moderate certainty of evidence) recommends against the use of sublingual immunotherapy in asthma treatment.”

In their discussion of SCIT, the Expert Panel has deleted a number of misleading statements present in the draft, but a few persist³:

“Delayed systemic reactions occur in approximately 15% of individuals after injection.” In the referenced article,⁴ it states: “When we focused on practices that monitor patients for at least 30 minutes, only 15% of SRs started after 30 minutes.” Thus, the Expert Panel statement should be “In approximately 15% of individuals who experience a systemic reaction, the reaction will start more than 30 minutes following the injection.”

“Incidence of fatal and near-fatal anaphylactic reactions has been estimated to range from 1 in every 20,000 to 1 in 200,000 injections.” In the referenced article,⁴ it states: “One grade 4 SR occurred in every 160,000 injections from 2012 to 2016. They occurred in 1 in every 20,000 treated patients.” The Expert Panel is confusing the frequency of events occurring per injection with the number occurring per patient.

“Incidence of fatal anaphylactic reactions has been estimated to range from 1 in every 2 million to 1 in every 9 million injections.” The Expert Panel is reporting rates that occurred in 2 different eras: the first was in the last 2 decades of the 20th century and the second in the first 2 decades of the 21st century.⁴ It is thought that changes in the practice of AIT, namely more attention to the state of control of patients’ asthma, probably accounts for this improvement.

In rejecting the use of SLIT, the Expert Panel provides a summary of the evidence, which also has some misstatements³:

“The evidence shows a trivial benefit for the critical outcomes that include asthma exacerbations, asthma control, and asthma quality of life.” This statement again raises the issue of what are the critical outcomes for AIT. A systematic review and meta-analysis of SLIT for adults with asthma⁵ published in 2018 found that “SLIT add-on therapy was associated with significant improvements in lower and upper airway scores, a higher FEV₁ and MEF₂₅₋₇₅, and improved bronchial hyperreactivity. Drug consumption was significantly decreased and airway inflammatory parameters were markedly improved.”

“The first study did not report on the number of exacerbations, but rather on the time to first exacerbation” Table II in the referenced study⁶ gives the number of participants and the number of participants with moderate or severe asthma exacerbations as well as a hazard ratio, which was significantly reduced with both doses of active treatment compared with placebo.

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“Four studies that evaluated asthma control using validated tools found no consistent improvement following treatment.” Of the studies cited, both de Blay et al⁷ and Wang et al⁸ reported significant improvement in these parameters in the subset of more severe patients. De Blay et al⁷ reported a reduction compared with placebo in the Asthma Control Questionnaire score of (–) 0.41 ($P = .0002$) from a baseline of 1.0 to 1.5 and in the Asthma-Related Quality of Life Questionnaire score of 0.52 ($P = .01$). Wang et al⁸ reported a higher percentage of immunotherapy—than placebo—treated patients with an Asthma Control Questionnaire score of less than 0.75 (56.5% vs 40.0%; $P = .039$).

Finally, under “Rationale” is the following statement³:

“In evaluating the data on aqueous or drop and tablet formulations combined, the Expert Panel did not find that SLIT reduced asthma symptoms or improved asthma control or asthma quality of life.” This is clearly in disagreement with their source document.² The summary statement of the Comparative Effectiveness Review Number 196, The Role of Immunotherapy in the Treatment of Asthma, summarized their conclusions on page 27 in regard to SLIT: “SLIT improves asthma symptoms, as measured by validated instruments (high strength of evidence (SOE)); SLIT improves disease-specific quality of life and decreases use of long-term control medication (specifically, ICS) and improves FEV₁ (moderate SOE); SLIT may decrease quick-relief medication use (short-acting bronchodilators) (low SOE).” Given the strength of these findings, it is difficult to agree with the Expert Panel conclusions recommending against the use of SLIT in the treatment of asthma.

The section on immunotherapy for asthma ends with a list of future Research Opportunities.³ One cannot argue with the need for addressing many aspects of immunotherapy and asthma, but the most crucial need for both SCIT and SLIT is for proof of efficacy and to a lesser degree of safety, of multiallergen AIT. The main proof for efficacy of multiallergen SCIT is the classic study by Douglas Johnson,⁹ but that was conducted with imperfect methodology in the 1950s and 1960s. There is no study

supporting the administration of true, multiallergen SLIT. On the contrary, the only study addressing the subject suggests that multiallergen SLIT might have diminished effectiveness.¹⁰ Who is to pay for the appropriate multiallergen AIT studies? There is little financial incentive for allergen extract companies, leaving the federal government or the national allergy societies the only ones in a position to meet this need.

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