Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs

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As required by the European Medicines Agency and the US Food and Drug Administration for pivotal trials involving allergen immunotherapy (AIT) products, clinical efficacy assessment is currently based on double-blind, placebo-controlled field studies with natural allergen exposure during the allergen season. However, this study design is associated with several drawbacks, such as the high variability of allergen exposure in different trial sites or seasons and the presence of confounding environmental factors. On the contrary, environmental exposure chambers (EECs) aim to operate with a stable and reproducible allergen exposure under highly standardized environmental conditions. Technical validation parameters for different EECs worldwide have been published by several groups. However, full clinical validation of EEC study outcomes is required for their classification as an appropriate alternative to natural allergen exposure for AIT product efficacy assessment. Some clinical validation parameters have already been addressed for EEC units. The reliability of provoked symptoms in repeated EEC sessions is high, but the predictive power of EEC settings for the clinical response on natural exposure and the impact of seasonal priming on test results still have to be validated systematically, as does the inter-EEC variability. Thus the authors recommend a continued in-depth validation of EECs to exploit the potential of this technology for future AIT product development. (J Allergy Clin Immunol 2015;135:636-43.)

Key words: *Environmental exposure chamber, allergen immunotherapy, clinical validation, pivotal studies*

Clinical testing of products for allergen immunotherapy (AIT) is traditionally conducted in clinical trials by using natural allergen exposure in an outpatient setting. However, the sensitivity, reproducibility, and comparability of such clinical trials are affected by the variability of airborne allergen exposure: pollen counts are subject to strong local, seasonal, and diurnal variations and affected by confounding environmental conditions, such as rain, temperature, humidity, and wind speed.[1-3] Furthermore, the actual individual pollen exposure is influenced by the respective subject's lifestyle (indoor/outdoor activity) and residence (urban/rural).[2-4] The reliability and reproducibility of such seasonal field studies also depends on the difficulty in defining and capturing the peak pollen season and individual variability in maintaining the study diary.[1-5] Thus only limited information regarding the onset and duration of action of an

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Abbreviations used
AIT: Allergen immunotherapy
AR: Allergic rhinitis
ARTSS: Average rhinoconjunctivitis total symptom score
EEC: Environmental exposure chamber
EMA: European Medicines Agency
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TNSS: Total nasal symptom score

investigational compound can be drawn from such natural exposure trials.[1,4,6]

The use of environmental exposure chambers (EECs) can overcome these drawbacks by means of defined, stable, and reproducible allergen exposure under highly standardized environmental conditions.[1,3,6] Furthermore, in allergic rhinitis (AR) trials EEC assessments exclude bias because of the use of rescue medication and enable controlled symptom scoring.[1-3,5,7,8]

EECs have been used for efficacy assessment and outcome evaluation in AR trials since the 1980s: Horak and Jäger[9] first reported the Vienna Challenge Chamber in 1987. At the same time, the Environmental Exposure Unit in Kingston, Canada, was established for AR research.[3,10] During the following decades, the EEC model was continually evolved, and additional facilities were established: the Fraunhofer Environmental Challenge Chamber in Hannover/Germany and smaller or primarily commercially operated EEC units in Denmark (Copenhagen), the United States (Atlanta), and Japan (Wakayma, Osaka, and Tokyo). The EEC setting has since been extensively used to evaluate the efficacy and safety of antiallergic medication (antihistamines/corticoids), with special emphasis on the onset and duration of action of these drugs.[11-23] These trials are reviewed by Day et al.[3]

Immunotherapy trials using the EEC system are first mentioned in the 1990s by Horak et al[24] and Donovan et al.[25] More recently, the effects of novel allergen products for both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) were evaluated by means of EEC challenge.[26-28] However, to date, the use of EEC settings in AIT trials is relatively low and generally limited to phase II trials. This can be attributed to the fact that until now the European Medicines Agency (EMA) and the US Food and Drug Administration do not recognize EEC trials without evaluation of efficacy during natural exposure as the primary end point as pivotal (phase III) studies.[29,30] However, the current EMA guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases[29] accepts the EEC model for efficacy analysis in dose-finding and pharmacodynamic studies.

Existing challenge chambers are technically validated and reported to operate within their specifications in terms of environmental conditions (eg, temperature, humidity, and air pressure) and allergen distribution. Moreover, the use of EECs as a promising outcome measure adjunct to natural pollen exposure in phase III trials is discussed in the recently published European Academy of Allergy and Clinical Immunology position paper on clinical outcomes used in allergen immunotherapy trials.[31] However, with respect to clinical validation of EECs, there are still basic questions to be answered, as pointed out by the EMA in 2008[29]: Is the treatment effect biased in out-of-season EEC sessions because of the lack of seasonal priming? How well does the EEC setting reproduce the real-life situation? In other words, how does the controlled allergen challenge compare with natural exposure?

This review article aims at summarizing and discussing published data on the validation status of EEC methods with respect to technical aspects and an emphasis on clinical validation. A focus will be on the unmet needs for validation from a clinical and regulatory point of view, especially regarding treatment outcome measurements in the EEC system.

TECHNICAL VALIDATION OF EXISTING EECs

Currently used pollen chambers have undergone systematic technical validations. The main cornerstones of technical EEC validation are homogenous spatial allergen distribution, temporal stability of allergen levels (intrasession and intersession), and stable, defined, and reproducible environmental conditions throughout an exposure session. Temperature, humidity, and volumetric air flow rate have to be monitored and kept within a narrow range of target values during the entire challenge.[2,3,7,10,32]

There are 2 standard methods for controlling and documenting spatial homogeneity and temporal stability of pollen levels: (1) Rotorod samplers positioned throughout the subject's seating area for offline measurement (calculating the pollen dispersal levels in the EEC retrospectively after completion of the exposure session)[3,32] and (2) laser particle counters for real-time determination (determining the actual pollen dispersal levels during the EEC session).[3,32]

Krug et al[32] found a strong correlation between the 2 methods in the Fraunhofer unit. Target pollen concentrations during a 4-hour exposure and from day to day showed only slight variations (day-to-day variation, 3.7% to 5.5%), with spatial distribution of pollen within the chamber varying by ±10%. Constant ragweed pollen levels over an 8-hour challenge period and reproducible pollen levels in 5 subsequent sessions have been shown also for the Kingston Environmental Exposure Unit[10]: the average daily ragweed pollen concentrations varied from the predefined level by less than 5%.

Ito et al[33] demonstrated that the pollen distribution in the EEC in Osaka varied from 80% to 110% of target dispersal values, and the rate of pollen level variations throughout an exposure session did not exceed 15%.

Published technical validation data of existing EECs are compiled in Table I.[2,3,10,15,23,32-37] The various technical setups and specifications of existing EEC facilities in Europe, Canada, and the United States have been reviewed by Day et al.[3]

In summary, existing EEC facilities have been reported as technically validated and proved to function within the predefined specifications. Thus it can be concluded that controlled and reproducible inhalation exposure to routine airborne allergens (eg, grass, tree, ragweed, mountain cedar, Japanese cedar pollen, and house dust mite) can be ensured. Furthermore, technical validation is in progress for new EEC setups, such as mobile EEC systems.

However, comparison of the results obtained in distinct units remains difficult because of the differences between physical setup and engineering features of worldwide existing facilities.

CLINICAL VALIDATION OF EXISTING EECs

Systematic clinical validation of EECs existing worldwide has not been conducted thus far. Only a few parameters