Original Article

Minimal Clinically Important Difference (MCID) in Allergic Rhinitis: Agency for Healthcare Research and Quality or Anchor-Based Thresholds?

Eli O. Meltzer, MD[a,b], Dana Wallace, MD[c], Mark Dykewicz, MD[d], and Lucy Shneyer, MA[e] *San Diego, Calif; Fort Lauderdale, Fla; St. Louis, Mo; and Denville, NJ*

What is already known about this topic? Multiple approaches have been suggested for estimating a minimal clinically important difference (MCID) for allergic rhinitis studies, with most based on the total nasal symptom score (TNSS). Most recently, in 2013, the Agency for Healthcare Research and Quality (AHRQ) in the USA recommended using an MCID equal to 30% of the maximum TNSS as a useful threshold. Treatment differences that failed this threshold would indicate equivalence. However, evaluations testing this threshold by the AHRQ and subsequent investigators could not demonstrate differences in effectiveness between various treatments for seasonal allergic rhinitis.

What does this article add to our knowledge? This article describes the use of a threshold determined using a validated anchor-based approach that can be applied to allergic rhinitis clinical studies with appropriate data. By applying this threshold to 3 of the queries in the AHRQ report, using that same database, the article demonstrates the differences in outcomes. MCIDs for patient symptom relief were attainable for the majority of studies, despite the negative results reported by the AHRQ. In contrast to the results of the AHRQ analysis, the outcomes shown in this article are those that would be expected based on other reports in the published literature, including current management guidelines.

How does this study impact current management guidelines? The MCID calculations using the validated anchor-based estimate reported here support most of the recommendations of current management guidelines. The finding that intranasal corticosteroid with intranasal antihistamine in the same device was more effective than either monotherapy alone should be carefully reviewed for future guidance documents. In addition, we believe that the approach used in this article currently represents the only reasonable method to determine an MCID for allergic rhinitis studies and should supersede the method and consequent findings of the AHRQ report.

BACKGROUND: In 2013, the Agency for Healthcare Research and Quality (AHRQ) recommended that allergic rhinitis (AR) studies calculate a minimal clinically important difference (MCID) based on an estimated threshold equal to 30% of the maximum total nasal symptom score. Applying this threshold, their data showed no differences between well-established treatments, and a subsequent analysis using prescribing information found no differences between active treatments and placebo controls.

OBJECTIVE: The objective of this study was to demonstrate the application of an evidence-based model to determine MCIDs for

[a]Division of Immunology and Allergy, Department of Pediatrics, University of California San Diego School of Medicine, San Diego, Calif

[b]Allergy and Asthma Medical Group and Research Center, San Diego, Calif

[c]Florida Center for Allergy and Asthma Control, Nova Southeastern University College of Health Professions, Fort Lauderdale, Fla

[d]Section of Allergy and Immunology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Mo

[e]Shneyer Statistics LLC, Denville, NJ

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Corresponding author: Eli O. Meltzer, MD, Allergy and Asthma Medical Group and Research Center, 5776 Ruffin Road, San Diego, CA 92123. E-mail: eliomeltzer@gmail.com.

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Abbreviations used
AHRQ- Agency for Healthcare Research and Quality
AR- Allergic rhinitis
AZE- Azelastine
BDP- Beclomethasone dipropionate
BL- Baseline
DB- Double blind
DD- Double dummy
FP- Fluticasone propionate
GRCS- Global rating of change score
INAH- Intranasal antihistamine
INCS- Intranasal corticosteroid
LOR- Loratadine
LTRA- Leukotriene receptor antagonist
MC- Multicenter
MCID- Minimal clinically important difference
MeSH- Medical subject heading
MON- Montelukast
MOM- Mometasone furoate nasal spray
mm- Millimeter
MP-AzeFlu- Azelastine+fluticasone propionate in a single device
OAH- Oral antihistamine
OLO- Olopatadine
P- Placebo
PC- Placebo controlled
PG- Parallel group
PM- Evening
QD- Once daily
R- Randomized
SAR- Seasonal allergic rhinitis
SD- Standard deviation
SLIT- Sublingual allergen immunotherapy
Sx- Symptoms
TNSS- Total nasal symptom score (r, reflective)
TSS4- Total symptom score 4 (another descriptor for TNSS)
Tx- Treatment
VAS- Visual analog scale

AR studies, with an absolute value for an anchor-based threshold and validated methods for calculating distribution-based thresholds.
METHODS: Using the same studies as the AHRQ report, anchor- and distribution-based MCID thresholds were determined for 3 clinical comparisons identified by the AHRQ: (1) oral antihistamine + intranasal corticosteroid (INCS) versus INCS, (2) montelukast versus INCS, and (3) intranasal antihistamine + INCS in a single device versus the monotherapies. The outcomes were compared with those reported using the AHRQ threshold.
RESULTS: No treatment comparison met the AHRQ-defined MCID threshold; all treatments were determined to be equivalent for all 3 queries. In contrast, the evidence-based model revealed some differences between treatments: INCS > montelukast; intranasal antihistamine + INCS > either monotherapy. No clinically relevant benefit was observed for adding an oral antihistamine to INCS, but some studies were not optimal choices for quantitative determination of MCIDs. Updating the literature search revealed no additional studies that met the AHRQ inclusion criteria.
CONCLUSIONS: The evidence-based threshold for MCID determination for AR studies should supersede the threshold recommended in the AHRQ report. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Allergic rhinitis; Oral antihistamine; Intranasal antihistamine; Intranasal corticosteroid; Leukotriene receptor antagonist; Minimal clinically important difference (MCID); Seasonal allergic rhinitis (SAR); Total nasal symptom score (TNSS)*

Evidence-based medicine integrates research outcomes, clinical expertise, and patient expectations to optimize clinical decision making during treatment. A key pillar of the evidence-based approach is the concept that, to be considered effective, a therapy should provide both statistically significant and clinically meaningful differences over a placebo and/or active comparators. What is clinically meaningful can be estimated through determination of a minimal clinically important difference (MCID), which is defined as the minimal amount of a treatment effect (or change) that is important to the patient.[1-4] How to measure this in a manner that incorporates the patient's perspective yet allows for appropriate comparison of different treatments is subject to discourse.

Multiple evidence-based methods for determining an MCID have been described, with most falling into 2 classes: anchor-based and distribution-based approaches. Both can be used to determine the magnitude of a clinically relevant treatment effect size from a population perspective that is, quantitatively, based on treatment group means.[1,2,5]

As named, the anchor-based approach links a change in a desired outcome measure to a "meaningful" external anchor that reflects the patient's perspective, such as the global rating of change score (GRCS) by which patients rate their impression of treatment.[1,2,6] For example, the patient might be asked to finish the statement, "Since starting therapy my symptoms are," using an ordinal scale from −7 (very much worse) to 0 (no change) to +7 (very much better).

Distribution-based approaches assess statistically significant changes in the desired outcome measure in relation to the probability of change occurring by chance. For example, a clinically meaningful effect might be defined as a change above an arbitrary multiple of the sample standard deviation (SD) for the measure at baseline.[1,2,6] Because distribution-based methods are sample specific, MCID scores can be determined by statistical analysis alone, even when a change from baseline is difficult to detect (eg, in studies with large sample sizes and variances).[2] However, unlike anchor-based approaches, distribution-based calculations are not necessarily linked to any patient perspective of a clinically meaningful response. Consequently, anchor-based MCIDs are generally considered more robust.[1,2,7,8]

Determining an MCID in allergic rhinitis studies

How MCID comparisons apply to clinical decision making varies by disease state.[1,2,7] For some, including allergic rhinitis (AR), how to calculate the MCID remains a point of discussion. To date few articles have addressed this issue for AR, and those that have—including guidances from government health care agencies in the European Union and the United States—suggest widely different approaches (see Appendix E1 available in this article's Online Repository at www.jaci-inpractice.org).[1,8-12]

For the patient, AR is a disease characterized by annoying symptoms, and, reflecting this, the most commonly used scale to