

Correspondence

Reply

To the Editor:

We thank Turner et al¹ for their interest in our article. They highlight that there is no consensus in the allergy community when defining adverse allergic events and the fact that there are several methods for grading the severity of systemic allergic reactions. We agree that these various approaches have the potential to create confusion in both clinical care and adverse event (AE) reporting for clinical trials. A clear understanding of the safety profile of a treatment is needed to accurately assess the risk-benefit ratio of any therapy, which is essential for clinicians, patients and caregivers, industry, and regulators.

Turner and et al¹ first question the terminology used when referring to "systemic allergic reaction" versus "anaphylaxis." A full explanation of these terms is given in the definitions provided in the Methods section and the Online Repository for our original article.² To summarize, the term *systemic allergic reaction* refers to an anaphylactic reaction event of any severity (as defined according to the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network [NIAID/FAAN] criteria³ and graded using the 3-point Muraro [European Academy of Allergy and Clinical Immunology] grading scale⁴). In contrast, the term *anaphylaxis* is used to distinguish a systemic allergic reaction that was graded as severe on the same Muraro scale.⁴

Although allergic reactions may not be consistently defined this way in clinical care, the regulatory agencies overseeing our trials suggested using this system to reduce ambiguity. We agreed with the regulators and have used the same definitions in previous publications.^{5,6} To further provide complete transparency to the reader, data on systemic allergic reactions (or anaphylactic reactions) and anaphylaxis are reported in Tables III and Tables E5 and 6 of our original article.² This information allows readers to make their own conclusions on safety, regardless of their preferred definition of anaphylaxis.

The letter also states that the use of the different grading scales (the Consortium of Food Allergy Research [CoFAR]-modified, Common Terminology Criteria for Adverse Events [CTCAE], and Muraro⁴ scales), and their "amalgamation for the assessment of systemic allergic reactions" may be confusing. To clarify, as stated in our article,² 1 grading scale was used for each of the 3 AE categories (nonallergic AEs, allergic AEs not meeting the modified NIAID criteria, and allergic AEs meeting the modified NIAID criteria). The CTCAE scale was used for nonallergic

AEs, the CoFAR-modified scale was used for those allergic AEs that did not meet the modified NIAID/FAAN criteria, and the Muraro scale was used for allergic AEs that met the modified NIAID/FAAN criteria (systemic allergic reactions, or anaphylactic reactions [as stated earlier in this reply]) (Table I). Importantly, the classification criteria and severity grading for AEs were predetermined before any data collection and agreed on with the regulators.

The single grading scale used to grade an AE was determined by the category of the AE. Therefore, systemic allergic reactions (or anaphylactic reactions) were consistently graded by using only the Muraro scale (and not as suggested, by using a combination of Muraro with CoFAR), and this approach is consistent in the current and previous publications.^{5,6} We do note that as in previous publications,^{5,6} the epinephrine use tables report outcomes from *all 3 different grading scales* (the CoFAR-modified, CTCAE, and Muraro scales), as explained in the footnotes of these tables.

Epinephrine use, whether in clinical trials or clinical practice, is an inconsistent marker of reaction severity.⁷ The letter suggests that "it seems incongruous that 80% of participants using epinephrine outside the hospital environment did so for nonanaphylaxis reactions." We strongly disagree with this and note that epinephrine use for treatment of allergic reactions varies by geography and clinical practice.⁷ Caregivers and patients use epinephrine following ingestion of allergen before onset of symptoms or to treat isolated urticaria or stomach discomfort or pain. Conversely, in our original article,² there were 2 patients reporting anaphylaxis (severe systemic allergic reactions) who were not treated with epinephrine (see Table E6). One of the benefits of the Muraro severity grading scale is that it does not rely on medication use, thus avoiding this confounding variable. Importantly, in our original article,² reporting of systemic allergic reactions (see Table III, E5, and E6) includes the Muraro scale and the use of epinephrine in these events (see Tables III and E6). Again, the aim here is to provide clinically relevant data that allow the reader to interpret those data as they see fit.

In summary, our article² provides a transparent, accurate, and factual summary of this extensive safety data set, using all of the available methods to evaluate allergic reactions. At present, there is no comprehensive and universal system to classify and grade systemic allergic reactions. Efforts from the food allergy community and numerous recent initiatives, including the update to the CoFAR Grading Scale for Systemic Allergic Reactions in Food Allergy and the new World Agriculture Organization

TABLE I. Summary of the AE severity grading scales used through this study and previous study reports

Category of AE (any severity or relation to drug)	AE severity grading scale used*	Scale
AEs that were not allergic (hypersensitivity) events	CTCAE version 5	1-5
Allergic (hypersensitivity) AEs not meeting modified NIAID/FAAN criteria	CoFAR-modified CTCAE	1-5
Allergic (hypersensitivity) AEs meeting modified NIAID/FAAN criteria	Muraro/EAACI ²	1-3
<i>Systemic allergic reactions or anaphylactic reactions</i>		Grade 1: mild systemic allergic reaction Grade 2: moderate systemic allergic reaction Grade 3: anaphylaxis (severe systemic allergic reaction)

CTCAE, Common Terminology Criteria for Adverse Events; EAACI, European Academy of Allergy and Clinical Immunology.

*Only 1 severity grading scale was used to grade each AE.

classification of anaphylaxis, are a reflection of progress toward a clearer classification. Indeed, it remains imperative that we continue to clarify different terms in a way that is useful for all stakeholders, including regulators, clinicians, and patients.

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studies before employment by Aimmune; she has a patent pending for US patent 16/721,805. D. Norval and A. Vereda are employees of Aimmune Therapeutics. D. C. Adelman was an employee of Aimmune Therapeutics at the time of writing of the original article, and he is currently a consultant for Aimmune Therapeutics; he has patents pending (US 16/542,198; PCT/US2019/046706; US 16/721,805; and PCT/US2019/067634). A. W. Burks has received research support, advisory board fees, and lecture honoraria/consultation fees from Aimmune Therapeutics. S. M. Jones reports advisory board fees from Aimmune Therapeutics and Food Allergy Research and Education (FARE); personal fees from DBV Technologies; and clinical trial grants from Aimmune Therapeutics, DBV Technologies, Astellas, Sanofi, Regeneron, FARE, Genentech, and the National Institutes of Health—National Institute of Allergy and Infectious Disease. T. Casale reports grant funding from Aimmune Therapeutics and has acted as chief medical advisor for FARE.

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