

Correspondence

Clarifying the categorization of anaphylaxis as an adverse event during oral immunotherapy

To the Editor:

Brown et al recently published a useful synthesis of pooled safety data from phase 3 clinical trials (and their extension studies) evaluating Palforzia (Aimmune Therapeutics, Brisbane, Calif).¹ We would like to make 2 comments.

First, attributing *any* anaphylaxis to a “systemic allergic reaction” and reserving the term *anaphylaxis* to refer only to severe anaphylaxis (according to Muraro et al²) is highly unusual. Having specifically identified those adverse events that met the study-defined definition of anaphylaxis, Brown et al¹ then alter that classification in their report, such that those anaphylaxis events that do not involve “hypotension, hypoxemia, or neurologic compromise”² are termed *systemic allergic reactions* (rather than anaphylaxis)—something that is potentially misleading. Unfortunately, Brown et al did the same in their original study reports,^{3,4} although we acknowledge that they do state this

upfront, and further, they justify this as being “consistent with guidance from the “US Food and Drug Administration.”¹ However, the risk is that readers who have not noted this detail might conclude that Palforzia-related anaphylaxis (according to the more conventional use of the term) is less frequent than it is.

Second, the amalgamation of 2 methods of categorization for treatment-related adverse events (TRAEs), namely, the use of Consortium for Food Allergy Research (CoFAR)-modified Common Terminology Criteria for Adverse Events (CTCAE) criteria³⁻⁵ and the method used by Muraro et al² for anaphylaxis, in their Table E3 (see the Online Repository of Brown et al¹ at www.jacionline.org) and elsewhere is potentially confusing.² In their current analysis, Brown et al¹ report 10 “severe” anaphylaxis events in their Table E6 (see the Online Repository of Brown et al¹ at www.jacionline.org), which by definition involve “hypotension, hypoxemia, or neurologic compromise”² and would seem to align best with CoFAR/CTCAE grade 4 reactions, in which “symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness” (see Table I).³⁻⁵ However, these 10 events do not appear as grade 4

TABLE I. Categorization of anaphylaxis events according to CoFAR-modified CTCAE criteria⁵ and the apparent categorization of such events by Brown et al¹

CTCAE grade	Guidance from Aimmune protocols and CoFAR ³⁻⁵	Categorization of anaphylaxis (according to Muraro et al ²) by Brown et al ¹	Comments
Grade 1: mild	Transient or mild discomforts (<48 h); no or minimal medical intervention/therapy is required. These symptoms may include pruritus, swelling or rash, abdominal discomfort, or other transient symptoms		
Grade 2: moderate	Symptoms that produce mild-to-moderate limitation in activity; some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting, or other symptoms	Moderate anaphylaxis: marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing, and retractions; crampy abdominal pain, recurrent vomiting, and/or diarrhea, and/or mild dizziness	
Grade 3: severe	Marked limitation in activity; some assistance is usually required; medical intervention/therapy is required, and hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) is usually indicated	Severe cyanosis or SpO ₂ value ≤ 92% at any stage, hypotension, confusion, collapse, loss of consciousness, or incontinence	CTCAE clearly state that parenteral medications (eg, IM adrenaline) are usually indicated for grade 3 reactions. Arguably therefore, most anaphylaxis reactions (referred to as systemic allergic reactions by Brown et al ¹) should be categorized as grade 3 reactions
Grade 4: life-threatening	Extreme limitation in activity; significant assistance and significant medical intervention/therapy are required. Hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia, with a resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms	None	Should “hypotension, confusion, collapse, loss of consciousness” be categorized as grade 4 rather than grade 3 reactions?
Grade 5: death	Death		

The system in Muraro et al² is a 3-point grading system.
IM, Intramuscular.

reactions in Tables E3 and E4 (see the Online Repository of Brown et al¹ at www.jacionline.org), implying that in the tables, the events may be listed as grade 3 reactions (perhaps because Muraro et al² used only 3 grades). This potential amalgamation of Muraro grade 3 events with grade 3 CTCAE events is again misleading, given the impression of these being of a lower CTCAE grade than they actually were.

There is similar ambiguity regarding the severity classification depicted in Fig 3 of Brown et al,¹ which reports that 16 participants (1.7% of 919) had a CTCAE “severe” (grade 3) reaction during up dosing (for which “parenteral medications are usually indicated”). However, in Table E4, 84 of 919 participants used epinephrine at least once to treat an adverse event. Although we acknowledge that some of these events might not have met National Institute of Allergy and Infectious Diseases criteria for anaphylaxis and that clinicians may choose to use epinephrine to terminate nonanaphylaxis reactions early, it seems incongruous that 80% of participants using epinephrine outside the hospital environment did so for nonanaphylaxis reactions. Because “parenteral medications are usually indicated” for anaphylaxis according to all international guidelines (wording that aligns with CoFAR/CTCAE grade 3 events), this implies that most anaphylaxis events were instead categorized as CoFAR/CTCAE grade 2 events (on par, for example, with truncal urticaria) for which “no or minimal intervention/therapy is required.”³⁻⁵ Notably, the most recent version of the CTCAE (version 5, published November 27, 2017) clearly states that anaphylaxis is, at the minimum, a grade 3 event.

These issues regarding TRAE categorization may not change the underlying message (ie, that anaphylaxis as a TRAE is uncommon and its frequency decreases with time), but the unintended distortion of the safety data is most unfortunate. Brown et al¹ conclude that their data “can be used by allergists, patients, and their families to facilitate a benefit-risk discussion”—but this requires unambiguous data that represent clinical reality. We would ask the authors to help clarify the aforementioned issues

and present their data using CTCAE and Muraro grades separately—as they did in their original reports.^{3,4} This would allow readers to interpret these safety data with greater clarity, facilitating more meaningful discussions with patients and their families as part of making shared decisions and obtaining informed consent.

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