Correspondence re: Randhawa et al, TIP's success in the treatment of cow's milk anaphylaxis leaves many questions unanswered

To the Editors:

The Tolerance Induction Program (TIP) reports a 99% success rate and adverse reaction (AR) rate less than 1% in more than 8000 patients[1]; to date, however, its methods have not been described in peer-reviewed literature. Oral immunotherapy (OIT) is promising but difficult, and thus, we read with interest the report by Randhawa and Marsteller[2] detailing unprecedented success treating patients with reported cow's milk (CM) anaphylaxis that was accomplished through ingestion of different mammalian species milk in combination with novel protocols created by artificial intelligence (AI).

The patient cohort achieving "success" had low-level sensitization to CM, as only 141 of 214 subjects had CM-specific IgE and 70 had a CM-specific IgE level less than 2.71kU/L. It is likely that many of these patients would tolerate CM without the TIP, and unfortunately, no entry OFC results were reported, which limits generalizability and likely overstates the efficacy of the TIP.

Randhawa and Marsteller[2] also failed to report accepted clinical indices of OIT efficacy, including time to maintenance dose, pass rates of the 4-g OFC and 10-g CM OFC, and dropout numbers. The TIP yielded an unprecedented 100% success rate, with an AR rate less than 1% and no dropouts. These results are markedly superior to those of other OIT trials, such as those seen with peanut OIT, in which case 95.2% of placebo recipients experienced an AR.[3]

The OFC numbers do not add up, raising questions regarding result validity. Reportedly, all 214 participants passed a 4-g total CM OFC and a 10-g CM OFC, which equates to a total of 428 OFCs. However, the adverse events section reported the following OFC numbers: 260 camel's milk OFCs, 154 mare's milk OFCs,114 donkey' milk OFCs, 110 sheep's milk OFCs, 194 goat's milk OFCs, and only 214 cow's milk OFCs. ARs were not stratified by animal species.

The manner in which Randhawa and Marsteller[2] describe their AI approach is obfuscating. They state that AI determined their OIT regimens, yet further specifics are lacking. In this and prior articles,[4,5] the Randhawa and Marsteller[2] report "machine learning–boosting algorithms," yet there are many different machine learning (ML) methods and ML-boosting algorithms available. It is standard to report the ML algorithm used, input features, model fine-tuning parameters, and outcome measurables. Performance metrics, such as accuracy, precision, or area under the curve should also be presented. The low numbers of ARs reported for the TIP would presumably make training such an ML model difficult.

In their report, Randhawa and Marsteller[2] assert that "the patient's markers are assessed into an endotype solely on the basis of applied mathematical arrays." There is no detail (eg, accuracy, reproducibility, or generalizability to outside populations) provided regarding the clustering methodology used. Although Randhawa and Marsteller[2] cite a previous publication as validation for their ML model,[5] it appears to be a generalized linear model in which the likelihood of peanut anaphylaxis was predicted almost entirely by peanut sIgE and peanut component testing. The many other tests performed were noninformative to the model.

We would welcome and encourage clarification by Randhawa and Marsteller[2] regarding the AI methodology and inclusion of traditional indices of OIT efficacy in their article. Without these essential points, it is impossible to draw meaningful conclusions from the article.

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