

## Allergic burden and response to dupilumab



To the Editor:

The *post hoc* analysis of Corren et al<sup>1</sup> looked at the response to dupilumab according to the criteria for allergic asthma based on eligibility for omalizumab, namely, a total serum IgE level of greater than or equal to 30 IU/mL and 1 or more perennial aeroallergen-specific IgE level of greater than or equal to 0.35 kU/L at baseline. The inference made here is that dupilumab works equally well in both allergic and nonallergic asthma. Pointedly, only 41% of the so-called nonallergic group had no history of allergic rhinitis and also tested negative for any aeroallergens. We feel these artificial criteria for allergic asthma may have blunted the ability to predict whether an increased atopic burden is associated with a differential response to dupilumab.

For example, in our regional multidisciplinary severe asthma meeting, we would not consider a specific IgE of say 0.4 kU/L along with a total IgE of say 40 IU/mL as being indicative of a prominent allergic phenotype. Hence, we would be interested to see a more appropriate breakdown for exacerbation reduction and improvement in FEV<sub>1</sub> for dupilumab versus placebo according to baseline total and specific IgE quintiles for the entire cohort or even as a continuous variable. In addition, it would be worth evaluating the response in those patients with 1, 2, 3, 4, 5, or more positive aeroallergen-specific IgE either perennial or seasonal. In other words, this would help to elucidate whether there is a significant putative relationship between increasing levels of nonspecific and specific atopy in predicting the response to dupilumab. It would also be meaningful to know whether increasing levels of atopy per se interact with type 2 inflammatory markers such as fractional exhaled nitric oxide and blood eosinophils. This would help clinicians better identify a particular phenotype that is likely to respond to dupilumab in a real-life setting.

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Conflicts of interest: B. Lipworth reports grants and personal fees from Regeneron, Sanofi, Mylan, and Teva; grants, personal fees, and nonfinancial support from AstraZeneca; other fees from GlaxoSmithKline; personal fees from Novartis during the conduct of the study and from Lupin, Glenmark, Vectura, and Cipla, outside the submitted work; grants, personal fees, and other fees from Boehringer Ingelheim; and that his son is an employee of AstraZeneca. R. Chan has nothing to disclose. C. Kuo reports personal fees from Pfizer, AstraZeneca, and Chiesi, outside the submitted work.

Received for publication October 14, 2019; accepted for publication November 8, 2019.

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- Corren J, Castro M, O'Riordan T, Hanania NA, Pavord ID, Quirce S, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract* 2020;8:516-26.

<https://doi.org/10.1016/j.jaip.2019.11.026>

## Reply



To the Editor:

We appreciate the correspondence from Lipworth et al<sup>1</sup> regarding our recent publication in *The Journal of Allergy and Clinical Immunology: In Practice* titled "Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma."<sup>2</sup> The diagnostic criteria used to define the allergic group in the article reflects clinical practice in the United States (minimum threshold of 30 IU of total IgE and specific IgE of 0.35 IU for perennial aeroallergens), with the exception of not having an upper limit of 700 IU for total serum IgE (because dupilumab therapy in adults is not weight based). There are limitations to this definition, which are acknowledged in the discussion section.

We welcome Lipworth et al's<sup>1</sup> suggestions for additional analyses in the allergic subgroup and assure them that we are working on many of these and other related analyses, with plans to publish the outcomes in the near future, with the caveat that small numbers for some of the subgroups may not have adequate statistical power.

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Conflicts of interest: J. Corren has received research support from Sanofi.

Received for publication November 7, 2019; accepted for publication November 8, 2019.

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<https://doi.org/10.1016/j.jaip.2019.11.025>

## Multiple drug hypersensitivity syndrome (MDH) should not be diagnosed by drug provocation tests



To the Editor:

The recent paper of Landry et al<sup>1</sup> summarizes the frequency and characteristics of multiple drug hypersensitivity syndrome (MDH) based on clinical data of 45 patients. The observation of MDH goes back to some short letters of Sullivan et al,<sup>2</sup> and has later been addressed and refined by Pichler et al in various reports.<sup>3,4</sup> It soon became clear that the term MDH is used for clinically and mechanistically different diseases and that it is important to make a distinction to drug-induced intolerance reactions from clearly immune-mediated MDH.<sup>3,4</sup> Therefore, we proposed to speak of MDH only if an immune-mediated mechanism was proven—either by skin testing or by *in vitro* tests, clearly distinguishing it from multiple drug intolerance reactions or flare-up reactions.<sup>3,4</sup>

The retrospective study of Landry et al reaches the diagnosis of MDH by using either skin tests (in 44.5%, n = 20) and drug

provocation tests (DPT) (in 55.5%,  $n = 25$ ).<sup>1</sup> In their conclusion, they recommend DPT as a tool to diagnose MDH.

We disagree with this conclusion: we consider DPT as not suitable for diagnosing MDH for 2 main reasons.

1. Although DPT is considered the gold standard for the diagnosis of drug hypersensitivity,<sup>5</sup> the authors' statement that it is "mandatory"<sup>1</sup> to diagnose MDH is problematic. MDH often includes patients with severe T-cell-mediated reactions.<sup>1,3,4</sup> To expose them again to the drug is ethically problematic. It is dangerous and contraindicated to perform DPT in such cases.<sup>5</sup>
2. DPT show whether a drug is tolerated or not under the condition used in DPT. The limitation of DPT, particularly in delayed reactions, such as role of dose, duration of re-exposure, and presence/absence of cofactors, has often been discussed.<sup>5</sup> The use of DPT in MDH is opposed by the fact that—in contrast to *in vitro* or skin tests—it does not provide a clue to the pathomechanism. A positive DPT may be triggered by the immune or nonimmune mechanism, and the crucial distinction of MDH as immune-mediated hypersensitivity is not provided by a positive DPT. The diagnosis of MDH by DPT thus inevitably leads to a mixture of patients with immunologically and nonimmunologically mediated reactions. Indeed, over half of the patients of Landry's study were included primarily based on DPT.<sup>1</sup> Particularly in patients with reactions to nonsteroidal anti-inflammatory drug (NSAID) and quinolones, pseudoallergic or intolerance reactions are just as likely.<sup>6,7</sup>

Consequently, we doubt the conclusion of Landry et al that immediate reactions occur so frequently in MDH, and that NSAID and quinolones are a frequent cause of MDH.<sup>1</sup> Because the next step in the description of MDH is a better understanding of its pathomechanism, it is of uppermost importance to rely only on patients who indeed have an immune-mediated MDH. This can be achieved by skin and even better by *in vitro* tests, but not by DPT.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication July 19, 2019; accepted for publication October 23, 2019.

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<https://doi.org/10.1016/j.jaip.2019.10.050>

## Reply



To the Editor:

We appreciate the interest of Jörg et al<sup>1</sup> in our paper. Although we agree that the term MDH is used for clinically and mechanistically different diseases (and most importantly and erroneously, it is extended to reactions nonevocative of DH), our series comprises patients with clearly proven DH, either allergic or not. We acknowledge that the authors have built their comment around the best characterized phenotype of MDH, namely the one associated with severe cutaneous adverse reactions (SCARs), for which they have published solid proofs. We did distinguish this phenotype of MDH in our original paper and we also pointed out that our series included only 17.7% (8 of 45) such patients, well described in Table II and throughout the text.

We use an internationally accepted classification,<sup>2</sup> included in the forthcoming International Classification of Diseases, Ninth Revision, of the definition of drug hypersensitivity and allergy.<sup>3</sup> The latter is when an immune mechanism is demonstrated by means of validated skin tests and/or immunological tests. The term intolerance is highly controversial, used by so many specialties, and some authors even propose to make it disappear from allergy publications.<sup>4</sup>

We agree with Jörg et al that the drug provocation test (DPT) in patients with SCARs is dangerous and not ethical. That is why we reported in Table II of our study that no patients with SCAR were explored by means of DPT, except patients 7 and 44, who both are discussed in depth in our article. Routinely, and according to international consensus,<sup>2</sup> we perform only drug allergy workup for drugs that are mandatory for patient health care such as beta-lactams, contrast media or nonsteroidal anti-inflammatory drugs (NSAIDs), general anesthetics, chemotherapeutics, and biologicals. Drugs tested by DPT in these 2 patients were deemed important therapeutic options, considering their allergic past and comorbidities. Moreover, DPT was performed in their cases according to an adjusted protocol, starting with low doses (1% of the therapeutic dose), with weekly incremental doses.

We also agree that making the diagnosis with a positive DPT leads to no data on the underlying mechanism, because of mixed immune and nonimmune reactions. However, this distinction is clinically irrelevant. When skin tests are negative, DPT still remains the gold standard for diagnosis of DH and MDH (in the absence of contraindications)<sup>2</sup> because of its clinical implication for the patient in case of a positive result, namely drug avoidance. In addition, some nonimmune mechanisms for NSAIDs are now well established.<sup>5</sup> This systematization is a fundamental characteristic of drug allergy/hypersensitivity.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication October 21, 2019; accepted for publication October 23, 2019.

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<https://doi.org/10.1016/j.jaip.2019.10.051>

## Patients who have anti-FcεRI nonreactive basophils do not represent patients with severe chronic spontaneous urticaria



A recent article by Oda et al<sup>1</sup> concluded that a low responsiveness of basophils via FcεRI reflects the disease activity in chronic spontaneous urticaria (CSU). Especially in a subgroup analysis of nonresponders (<10% CD203c<sup>high</sup> basophils by the basophil activation test) and responders (>10% CD203c<sup>high</sup> basophils), the nonresponders had a significantly higher urticaria activity score 7 (UAS7) and lower urticaria control test (UCT) scores than the responders. We did the same analyses using a total of 30 Japanese patients with CSU including 17 responders and 13 nonresponders (Tables E1 and E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). We found that there was no significant difference in UAS7 between the responders and nonresponders, and that the nonresponders had significantly higher UCT scores than the responders ( $P = .0433$ , Figure 1, A and B). Rauber et al<sup>2</sup> showed no significant difference in UCT scores between responders and nonresponders. The means  $\pm$  standard deviations for UAS7 were  $17.08 \pm 12.09$  and  $25.57 \pm 12.10$  in Oda et al's and our studies, respectively. Although the mean severities of the patients with CSU in both studies were moderate,<sup>3</sup> our patients with CSU tended to have a greater disease severity. Note that the responders in our study included 5 patients with a UAS7 of 42 (Figure 1, A, and Table E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

Oda et al<sup>1</sup> demonstrated that the duration of disease was significantly shorter among nonresponders than among responders. In our (Figure 1, C) and Rauber et al's studies,<sup>2</sup> no significant difference in the disease duration was seen between the 2 groups. Oda

et al also showed a significant correlation between the disease duration and the proportion of CD203c<sup>high</sup> basophils in patients with CSU. In our study, however, no significant correlation between these 2 factors was found (Figure 1, D).

Oda et al<sup>1</sup> compared the proportions of CD203c<sup>high</sup> basophils among patients with CSU classified into 3 groups based on their UAS7 and healthy controls (HCs). Their classification into 3 groups according to UAS7 (UAS7 0-6, mild; 7-15, moderate; 16-42, severe) is not common. Following Hawe et al's classification,<sup>3</sup> we used the following classification: UAS7 0, free; 1-6, well-controlled; 7-15, mild; 16-27, moderate; 28-42, severe (Table E3, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Using this classification, we compared the proportions of CD203c<sup>high</sup> basophils among patients with CSU classified into 4 groups based on UAS7 and HCs. We confirmed their findings that the proportion of CD203c<sup>high</sup> basophils was significantly lower in the severe group than in the HCs, when stimulated with anti-human IgE antibody (clone E124-2-8D, from Allergen kit [Beckman Coulter, Tokyo, Japan];  $P = .0049$ , Figure 1, E). Although Oda et al showed that there was no significant difference between the severe group and the HCs; when stimulated with anti-FcεRI antibody (clone CRA1), the proportion of CD203c<sup>high</sup> basophils was significantly lower in the severe group than in the HCs in our study ( $P = .0311$ , Figure 1, F).

Taken together, we agree with their findings, which show that the responsiveness of basophils via FcεRI was significantly lower in the severe group than in the HCs. However, it is difficult to conclude that nonresponders represent patients with severe CSU.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication November 5, 2019; accepted for publication November 28, 2019.

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<https://doi.org/10.1016/j.jaip.2019.11.032>