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Dupilumab and atopic march; Reduction of incident allergic events or Clinical control?

Dupilumab y marcha atópica; ¿Reducción de reacciones alérgicas o control clínico?

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To the editor:

The article by Geba et al., entitled "*Attenuating the atopic march: Meta-analysis of the dupilumab atopic dermatitis database for incident allergic events*",[1,2] published in *JACI 2023 Mar; 151 (3): 756-766*, offers insights into the potential of dupilumab in modulating the atopic march. The author's comment: "*...Dupilumab reduced the risk of new/worsening allergies by 34% (IRR 0.66; 95% confidence interval [CI], 0.52-0.84) and new allergies by 37% (IRR: 0.63; 95%CI: 0.48-0.83) versus placebo*", and "*...These treatment benefits did not reverse on treatment discontinuation in off-treatment follow-up*". Although the results are interesting, the study presents some methodological and conceptual aspects that call to be cautious with interpreting the results.

- The study's primary objective was *"...to determine the rate of acquisition of new or worsened allergic events for dupilumab versus placebo in patients with AD*". However, the use of dupilumab may mask symptoms of different allergic conditions, and these may only become evident after therapy discontinuation.[3] Despite the authors' claim that "*These treatment benefits did not reverse on treatment discontinuation in off-treatment follow-up*," when reviewing information about "*off-treatment period*" in Figure E3 we observe that the confidence interval of all studies crosses 1 and, additionally, the incidence rate ratio (IRR) was 0.99 (CI 95% 0.62-1.59.) Therefore, these results do not support the previous affirmation.

- Table E1 reveals a follow-up time of 16 to 52 weeks in the studies. Within this short period and considering predominantly adult patients, the observed variation in allergic events between dupilumab and control groups appears more attributable to disease control than a genuine reduction in incidence.

- The main result of the study present in Figure 3 "*Dupilumab reduced the risk of new/worsening allergies by 34% (IRR 0.66; 95% confidence interval [CI], 0.52-0.84) and new allergies by 37% (IRR 0.63; 95% CI, 0.48-0.83) versus placebo*." Of the 12 studies included in the Forest plot A and B, 11 crosses 1. Additionally, a single study (R668-AD-1224) does not

cross 1 and contributes with 47.6% of the weight, dragging down the observed significance. This may be due to the ecological fallacy, where aggregate analyses are interpreted but not the interindividual variability of patients.[4] Also, lack of bias assessment and publication verification reduces the reliability of the study's findings.

- It is not clear how the authors defined some terms used in the article as "*allergic conditions*", "*chemical allergy*", "*metal allergy*", "*contact dermatitis*", "*asthma*", and "*wheezing*". The lack of clarity in the definitions generates a risk of ambiguity fallacy.[5]

- It´s controversial that all conditions included in the study are really part of the atopic march. For example, authors included "*pruritus*" and "*urticaria*" as different diseases and assume thar are related with atopic march which is controversial.

- How was pet's allergy defined? While biologics may suppress specific IgE responses, their influence on clinical outcomes is not adequately addressed.

In summary, we thank Geba et al. for raising an interesting question about the impact of dupilumab on the atopic march. The question remains largely unanswered, underscoring the importance of future studies for a comprehensive understanding of biologics' effects on the atopic march.

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