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The association between baseline IgE level and urticaria control at six months of omalizumab treatment in chronic urticaria

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Key words

Omalizumab; urticaria; IgE level; D-dimer level; antihistamines.

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Impact statement

Poorer urticaria control at six months of omalizumab treatment in CU was not associated with baseline IgE level but was associated with shorter CU duration.

Summary

Background. *There is limited data on the use of baseline IgE level as a predictor of omalizumab response in chronic urticaria (CU). The aim of the present study was to determine if baseline serum total IgE level is associated with response at six months of standard-dose omalizumab.* ***Methods.*** *The study was designed as a retrospective, single-center, cohort survey. This observational real-life study included CU patients receiving omalizumab from September 1, 2014, to July 31, 2022 at a tertiary care allergy center. The control of urticaria was determined by the urticaria control test in the sixth month.* ***Results.*** *A total of 159 patients were enrolled in the study. All patients had received standard-dose omalizumab for six months. At the end of the treatment period, 126 (80%) patients were under control. The median of baseline IgE level was similar in controlled and uncontrolled patients. The baseline D-dimer level and regular antihistamine use during omalizumab treatment use were significantly higher, and CU duration at baseline was shorter in the uncontrolled group (p = 0.03, p = 0.02, p = 0.003, respectively). ROC analysis revealed that CU duration at baseline was related to urticaria control (AUC 0.665, 95%CI [0.586-0.738]).* ***Conclusions.*** *The results of the present study showed that urticaria control at six months of omalizumab treatment in CU was not associated with baseline IgE level but was associated with CU duration at baseline. The shorter CU duration was associated with poorer urticaria control in the sixth month of omalizumab.*

Introduction

Chronic urticaria (CU) is a disease that persists for more than six weeks, with itchy and edematous papules/plaques, and manifests with angioedema due to deep dermis or subcutis involvement, or both (1). The prevalence varies between 0.5-1% (2). It is recommended to use a standard-dose modern 2nd generation H1-antihistamines (sgAHs) as the first-line symptomatic treatment (3). Second generation H1-antihistamines have been used for many years because they are easily available, cheap, and safe, and up to fourfold increase in standard-doses is recommended in cases with insufficient response (4). However, more than 25% of cases are resistant to high-dose sgAHs, and it is recommended to initiate omalizumab as a second-line treatment in patients who do not respond to high-dose sgAHs (5). Patients with CU who do not get sufficient benefit from omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher dose, shorter intervals, or both (5). It is unpredictable which patients will not respond well to standard-dose omalizumab treatment. Although baseline IgE level was not correlated with severity of CU in the study of Baek *et al.*, low IgE level was correlated with severity of CU in the cohorts of Asero and Bhati *et al.* (6-8). Currently, there is limited data on baseline IgE level that can be used as a predictor of uncontrolled urticaria (urticaria control test [UCT] score below 12) in patients receiving standard-dose omalizumab. The aim of the present study was to examine the associ-

ation between baseline IgE level and urticaria control in patients receiving standard-dose omalizumab for six months.

Materials and methods

Study design and participants

The study was designed as a retrospective, single-center, cohort survey. This real-life study included a total of 159 CU patients receiving omalizumab from September 1, 2014, to July 31, 2022 at a tertiary care allergy center. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (2024/03-03). The study protocol was reviewed and approved by (Hacettepe University Ethical Committee), approval number (2024/03-03). Written consent of the participants was not required by Hacettepe University Ethical Committee. The study has been granted an exemption from requiring written informed consent, this decision was made by Hacettepe University Ethics Committee (2024/03-03). Inclusion criteria were provision of written informed consent, age ≥ 18 years, and use of omalizumab for six months due to CU (**figure 1**). Omalizumab was initiated in patients who did not respond to high-dose sgAHs within 2-4 weeks. Patients with other dermatological diseases or urticarial vasculitis were excluded from the study.

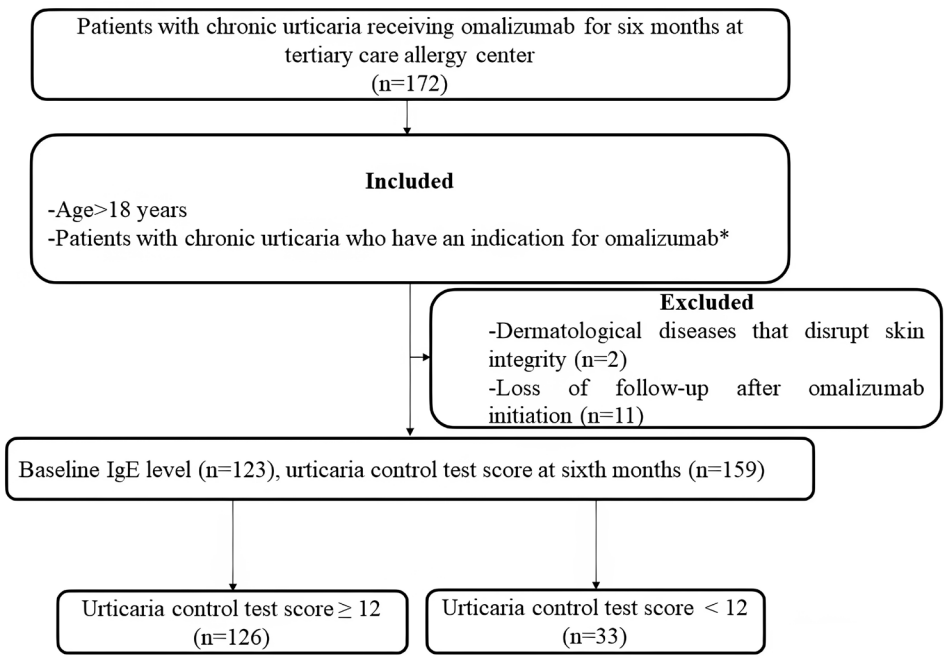
Data collection and laboratory measurements

Information about the clinical characteristics and laboratory values of the patients were obtained from the hospital database and patient files. In addition to the demographic characteristics of the patients, duration of CU, the presence of angioedema, allergic diseases, urticaria exacerbations requiring systemic corticosteroids in the last six months while receiving omalizumab, emergency room admissions because of urticaria attacks, omalizumab doses and intervals, comorbidities, medications, antinuclear antibody (ANA), IgG-anti-thyroidperoxidase (IgG-anti-TPO), specific IgE level and/or skin prick test results, blood eosinophil counts, blood basophil counts, C-reactive protein level, erythrocyte sedimentation rate, D-dimer and total IgE levels at baseline, and UCT scores in the sixth month were recorded. Serum total IgE was measured by a chemiluminescent immunoassay (ImmunoCAP; Thermo Fisher Scientific, Sweden), and the cutoff value of low IgE level was < 43 IU/mL (9).

Assessments of the treatment responses

Whether the disease was under control or not in the last month was determined by the UCT at the sixth month of therapy. Those with scores < 12 points were regarded as uncontrolled, and those ≥ 12 points were regarded as controlled (10). The UCT has been validated by Kocaturk *et al*. (11). In patients who were unresponsive or partially responsive to high-dose sgAHs and had the diagno-

Figure 1 *- The flow chart of the study (5).*



sis of CU confirmed by an allergy specialist, standard-dose omalizumab was initiated considering the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline (12).

Statistical analysis

Data were analyzed using SPSS vn. 25.0 software. Descriptive data were presented as numbers (n) and percentages (%). Numerical variables showing normal distribution were stated as mean ± standard deviation values, and otherwise as median and interquartile range values. The Chi-Square or Fisher Exact test for categorical variables and the Mann-Whitney U test for continuous variables were used. Spearman correlation coefficient was used for non-normally distributed parameters. For the multivariate analysis, factors identified through univariate analyses – including baseline CU duration, regular antihistamine use during omalizumab treatment, systemic corticosteroid use for urticaria attacks in the past six months, and D-dimer levels – were further included in the logistic regression analysis to determine independent predictors of patient outcomes. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was

Table I *- Comparison of baseline characteristics of the patients regarding urticaria control in the sixth month of omalizumab treatment.*

Characteristics*	**All patients (n = 159)**	**Controlled group (n = 126)**	**Uncontrolled group (n = 33)**	**P-value**
Age, mean years	44 ± 14	44 ± 21	45 ± 19	0.62
Female, n (%)	100 (63)	80 (63)	20 (61)	0.76
Obesity[1], n (%)	41 (26)	32 (25)	9 (27)	0.83
Ever smoker, n (%)	87 (55)	76 (60)	11 (33)	0.38
Types of chronic urticaria**, n (%)	151 (95)	120 (95)	31 (94)	0.65
CSU	4 (3)	3 (2)	1 (3)	0.48
CındU	4 (3)	3 (2)	1 (3)	0.25
CSU + CındU				
Chronic urticaria duration at baseline, median months	24 (78)	27 (86)	12 (24)	**0.003**
Regular antihistamine use during omalizumab treatment, n (%)	96 (60)	70 (55)	26 (79)	**0.02**
Presence of angioedema, n (%)	105 (66)	84 (66)	21 (64)	0.74
Systemic corticosteroids use due to urticaria attack in the last six months, n (%)	38 (24)	26 (21)	12 (36)	0.06
UCT, median	15 (2)	16 (1)	8 (4)	**<0.001**
Blood eosinophil count[a], median /mm³	107 (160)	100 (170)	100 (150)	0.97
Blood basophil count[a], median / mm³	8 (95)	5 (95)	5 (40)	0.54
C-reactive protein level[a], median mg/dl	0.2 (0.01)	0.32 (0.67)	0.36 (1.04)	0.72
Erythrocyte sedimentation rate[a], median mg/dl	4 (3)	1 (10.3)	1 (2.5)	0.57
D-dimer level[b], median mg/dl	0.20 (0.1)	0.20 (0.3)	0.27 (0.01)	**0.03**
ANA positivity, n (%)	4 (3)	3 (2)	1 (3)	0.83
Anti- TPO positivity, n (%)	14 (9)	16 (13)	5 (15)	0.71
Sensitization to inhalant allergens, n (%)	22 (14)	16 (13)	6 (18)	**0.007**
Baseline IgE level[c], median UI/mL	165 (289)	166 (259.5)	121 (356.5)	0.90
Low IgE[c], n (%)	14 (9)	11 (9)	3 (9)	1.00

*Data is presented as mean ± SD if normally distributed, and median [interquartile range] if not normally distributed. Categorical variables are Presented as number (percentages). **Types of urticaria are described CSU: chronic spontaneous urticaria, CındU; chronic inducible urticaria.

[1]Body mass index ≥30 kg/m². [a]Measured in 127 (80%) patients. [b]Measured in 112 (70%) patients. [c]Measured in 123 (77%) patients (29 [88%] of them in the uncontrolled group, 91 [72%] in the controlled group, and the cutoff value of low IgE level was < 43.8 UI/mL).

Figure 2 *- The association between the baseline IgE level and control of urticaria in the sixth month of omalizumab treatment.*

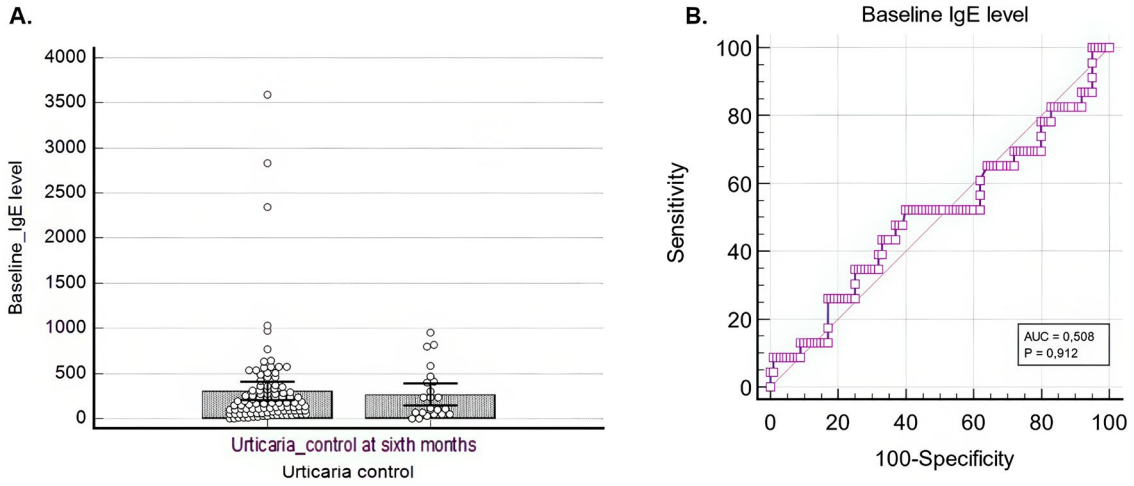


Table II *- Variables associated with uncontrolled urticaria in the sixth month of treatment, multivariable analysis.*

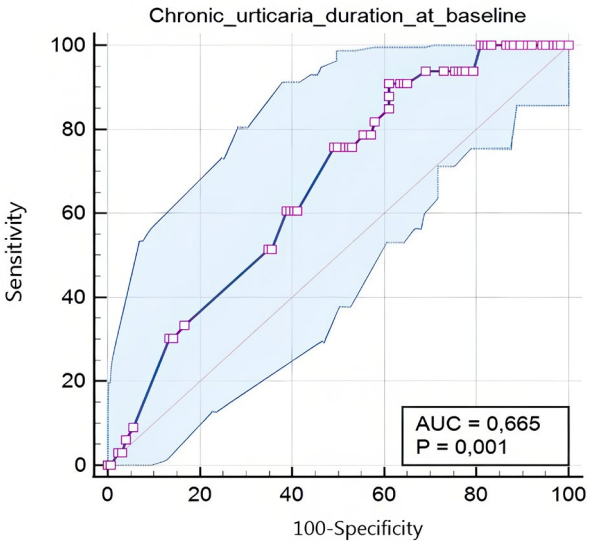
	OR	95%CI		P-value
Chronic urticaria duration at baseline, months	0.986	0.974	0.999	**0.03**
Regular antihistamine use during omalizumab treatment	3.095	1.036	9.247	**0.04**
Systemic corticosteroids use due to urticaria attack in the last six months	1.228	0.452	3.340	0.69
D-dimer level, mg/dl	1.191	0.629	2.255	0.60

used to inferstatistical significance. ROC analysis was done to assess baseline IgE level and CU duration at baseline as predictors of uncontrolled urticaria.

Results

Throughout the study period, 11 (6%) patients were lost to follow-up as they did not attend their appointments. Therefore, a total of 159 patients were enrolled in the study (**figure 1**). The mean age of the patients was 44 ± 14 years, and 100 (63%) of them were female (**table I**). All patients received standard-dose omalizumab for six months. In the sixth month of omalizumab, urticaria was under control in 126 (80%) patients. The median of baseline IgE level was similar in controlled and uncontrolled patients (**figure 2**, **table II**) (p = 0.73). Sensitization to inhalant allergens was higher in the uncontrolled group. Baseline median D-dimer level, and regular antihistamine use during omalizumab treatment were significantly higher in the uncontrolled group. The other characteristics such as female gender, presence of angioedema, baseline eosinophil counts and blood basophil

Figure 3 *- The ROC analysis for predictors of urticaria control score based on chronic urticaria duration at baseline.*



counts, ANA positivity, IgG-anti-TPO positivity, and comorbidities were similar in both groups (**table I**).

CU duration at baseline was significantly shorter in the uncontrolled group (**table I**). ROC analysis revealed that CU duration at baseline was related to urticaria control in the sixth month (AUC 0.665, 95%CI [0.586-0.738]). If the cutoff is selected as fifty-three months, estimated sensitivity and specificity is 90.91% (75.7-98.1) and 38.89% (30.3-48.0), respectively. If the cutoff for baseline urticaria duration was selected as eighteen months, estimated sensitivity and specificity was 60.61% (42.1-77.1) and 61.11% (52-69.7), respectively (**figure 3**). While this AUC suggests limited predictive strength, it highlights that chronic urticaria duration alone may not strongly predict control outcomes. However, this factor could still contribute valuable context within a comprehensive clinical assessment when considered alongside additional clinical variables.

In multivariable regression analysis model, independent risk factors for uncontrolled urticaria in the sixth month were CU duration at baseline and regular antihistamine use under omalizumab therapy (Nagelkerke R^2 = 0.214, **table II**).

Discussion and conclusions

The results of our study show that the control of urticaria in patients receiving omalizumab for six months is not related to baseline IgE level. CU duration at baseline and regular antihistamine use throughout 6 months are independently related to the control of urticaria.

Balp *et al.* pointed out that the cumulative proportion of patients undergoing remission within year 1 ranged from 21% to 47%, while at year 5, it was reported as 34% and 45%. There is some uncertainty about defining remission in urticaria (13). The differences in the rates arise from the uncertainty of the concept of remission in urticaria. While some authors define the absence of urticaria without treatment in the last 3 months as remission, some others consider it as patients reporting the absence of urticaria based on responses on self-reported questionnaires (13-15). Urticaria was under control at the sixth month in 80% of the patients in our study, but this treatment response may decrease when omalizumab injection intervals are extended, the dose is reduced, or treatment is discontinued. On the other hand, a significant proportion of these patients may also be in spontaneous remission and omalizumab may not have contributed to remission in these patients (16). As noted in the study by Marcus *et al.*, some patients with CU can achieve remission by the sixth month even without treatment, suggesting that the optimal evaluation period for treatment response in those who do respond may be extended to this time point (17). Consequently, the choice to assess treatment response at 12 weeks in some studies may have resulted in certain patients who would respond between the third and sixth months being classified as non-responders (18-20). We did not evaluate the treatment process after the sixth month of omalizumab.

CU duration at baseline and regular antihistamine use throughout 6 months of therapy are independently related to the control of urticaria. Unlike our cohort, Chen *et al.* described a tendency of longer disease duration in non-responders (21). In the study conducted by Chen *et al.*, a smaller sample size was included (138 patients in total), with 25% of patients presenting with only CIndU and an additional 13% having CSU accompanied by CIndU, which is higher than in our cohort. Treatment response was evaluated at the 12th week, with a response rate of 70%, which was lower than in our study. Additionally, 27% of these patients used methotrexate or cyclosporine in addition to omalizumab. The similarity in CU duration at baseline between responders and non-responders may be attributable to the duration of other treatments received before omalizumab initiation, potentially explaining the similar disease duration found, in contrast to our patients. Other studies did not support the relation between CU duration at baseline and treatment response (18, 22). However, in the studies by Cakmak *et al.* and Yang *et al.*, fewer patients were included (130 each), with a significantly higher proportion of CIndU cases compared to our study (20% and 17%, respectively). In both studies, the higher prevalence of CIndU patients – 20% and 17%, respectively – likely influenced the relationship between CU duration at baseline and disease control, as the treatment response rates for these patients were lower compared to those with only CSU. In the study by Ertas *et al.* involving 93 patients with CSU, the relationship between IgE levels and response to omalizumab was investigated. The non-responder rate was found to be 14%, and CU duration at baseline was higher in non-responders compared to responders (19). However, these patients discontinued omalizumab and were monitored for relapse over a 52-week period. In the multicenter, retrospective study by Marzano *et al.*, which included 470 patients comparing responders and non-responders to omalizumab, no significant differences were found in CU duration at baseline; however, treatment response was evaluated at the 12th week. Furthermore, the patients in their study were older (median age 49 *vs* 44) and had shorter CU duration at baseline (20 months *vs* 24 months) compared to our cohort (20). As expected, the rate of regular antihistamine use during omalizumab treatment was higher in uncontrolled patients. EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines recommend daily use of sgAHs to prevent the occurrence of wheals and angioedema, rather than on demand (5). Although it is not in accordance with the guidelines, some of our controlled patients (45%) do not comply with the recommendation and used antihistamines on demand.

Similar to our study, Ghazanfar e*t al.* evaluated 117 patients and showed no association between baseline IgE level and control of

urticaria at third month of omalizumab. Moreover, non-responders had a shorter urticaria duration. Unlike our study, 10% of the patients had received immunosuppressive drugs (azathioprine, methotrexate or cyclosporine) for urticaria before omalizumab (23). In a retrospective study, including 71 patient-year experience, while 57% of individuals showed a complete response within the first week, 80% had a complete response during follow-up. In this study, the omalizumab dose and/or intervals were changed after remission, and no correlation was found between urticaria control and baseline IgE level (24). Contrary to our study, Cakmak *et al*. found an association between low baseline IgE level and uncontrolled urticaria in the sixth month of omalizumab, but responders had a higher atopy (73% *vs* 4%) rate and, therefore, higher baseline IgE levels than our cohort (39% *vs* 13%) (22). In fact, there are some differences in the literature regarding threshold values for low IgE, defined as levels below 15.2 to 43 IU/mL (9, 25-27). In the study by Marzano *et al.*, a threshold value of 100 kUA/L was used for high IgE levels, while no clear cutoff was specified for low IgE levels. Additionally, the average IgE level among non-responders was found to be 42.1, which is above the accepted limit for low IgE according to some publications, while below the threshold in others (9, 25-27). Some studies showed an association between low IgE level and unresponsiveness to omalizumab (7, 27-29). Asero *et al.*, in their study of 86 patients with CSU and low IgE levels, categorized patients into subgroups based on baseline IgE levels as follows: Group A, total IgE levels 1-9 IU/mL (n = 28); Group B, IgE 10-19 IU/mL (n = 24); Group C, IgE 20-29 IU/mL (n = 22); and Group D, IgE 30-39 IU/mL (n = 12) (29). Group A had the highest proportion of non-responders to omalizumab at month 4 (64.3%; $p < 0.001$ *vs* subgroups B-D) and the lowest proportion of rapid responders (21.4%; $p < 0.005$ *vs* subgroups B-D). This study indicated that in patients with CSU, a lower IgE value, particularly those with levels below 10 IU/mL, may more effectively predict non-responders to omalizumab compared to the conventional cutoff of 40 IU/mL. Additionally, despite 46% of the patients having atopic status, they comprised 42% of the group with IgE levels below 40 IU/mL. The discrepancy may be due to the atopic status, the rates of chronic urticaria subtypes in the study populations, and different cutoffs of low IgE level. Yang *et al*. found higher baseline IgE level was associated with early response to omalizumab (263.0 *vs* 140.0 IU/mL). However, duration of the treatment was limited to one month (18).

Previously, a higher D-dimer level was defined as a predictor of uncontrolled urticaria after omalizumab treatment (30). In our cohort, baseline D-dimer level was higher in uncontrolled group, however D-dimer level was not found to be a predictor in multivariable analysis. Furthermore, in the study by Asero *et al.*, CSU patients with low IgE levels were included, and these low IgE values were divided into subgroups (29). However, no differences were found between any subgroup in terms of elevated D-dimer and urticaria control.

It was reported that autoimmunity might be a predictive factor for unresponsiveness to omalizumab therapy (21, 31, 32). However, baseline ANA and anti-TPO values were similar between groups in our study. In total, 13% and 15% of patients in the controlled and uncontrolled groups had high anti-TPO titers at baseline. The importance of this result lies in the indication that patients may respond well to omalizumab treatment even if they have positive anti-TPO titers.

This study has several limitations. It was designed retrospectively. Additionally, due to the uneven distribution of the cohort, it was not possible to categorize patients into chronic inducible urticaria and chronic spontaneous urticaria groups for urticaria control assessment. Our results can be re-evaluated with a larger cohort, but our findings are important. Further researches are needed to investigate the mechanism by which the response to omalizumab is weaker in patients with a shorter duration of urticaria at baseline.

In conclusion, the control of urticaria is not associated with baseline IgE level but with CU duration at baseline. In addition, the baseline IgE level does not seem to be determinative for predicting treatment outcomes with omalizumab.

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Contributions

GT, MD: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review & editing. ED, MD: conceptualization, data curation, validation, writing – review & editing. GK, MD: data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review & editing. AFK, MD: conceptualization, data curation, methodology, validation, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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