

LETTER

Prophylactic steroid use is ineffective in food allergy: A randomized-controlled clinical trial and a murine model

To the Editor,

Glucocorticoids (GCs) are widely used to prevent and treat anaphylaxis. However, no clear evidence exists to support its prophylactic use.¹ In addition to the classical genomic mechanism, GCs exert rapid non-genomic anti-inflammatory effects within a few minutes.²

We conducted a randomized-controlled trial (RCT) administering GC immediately after oral food challenge tests (OFCs) provoked mild skin symptoms in patients with food allergies (FA). The RCT was conducted from August 2018 to December 2021 and included 103 patients with a skin symptom score of 10 with or without any organ score of 1 according to the Anaphylaxis Scoring Aichi³ at OFCs. They were randomly divided into groups with and without administration of 1 mg/kg of prednisolone in addition to antihistamines for both groups (Table S1, Figure S1, and Methods S1). The proportion of worsening of 10 or more points, which we set as the primary outcome was not significantly different between the prednisolone- and prednisolone+ groups in both intention-to-treat (RR = 1.11, 95% CI = 0.39–3.03) and per-protocol (RR = 1.25, 95% CI = 0.43–3.48) analyses (Tables 1 and 2). Moreover, worsening scores, the proportion of any worsening, and additional medication use were not different (Table 1; Figure S2). Even when stratified by antigens used in the OFC (Table S2), organs showing worsening after intervention (Table S3 and S4), or sex (Table S5), the results were not changed. Though the time to take medications was longer in prednisolone+ than in prednisolone- (Table S1B), there was no correlation between the time and worsening scores (Figure S3). Overall, prednisolone did not exert rapid effects to protect from exacerbation of FA symptoms.

Further, we conducted murine models of anaphylaxis to determine the rapid effect of GCs in preventing anaphylaxis and reducing FA symptom exacerbations using the active systemic anaphylaxis, passive cutaneous anaphylaxis, and FA models^{4,5} (Methods S1). In these experiments, GCs (hydrocortisone, prednisolone, or betamethasone) were administered immediately before the antigen challenge and the symptoms were compared between the sham and GC-treated groups. Though hydrocortisone suppressed diarrhea mildly and tended to inhibit mast cell protease-1 level in the FA model (Figure 1), body temperature decline was not prevented in all models (Figure 1 and Figure S4). Additionally, the prophylactic use of prednisolone or betamethasone did not prevent any symptom exacerbations. Hydrocortisone has a stronger mineralocorticoid (MC) activity than prednisolone and betamethasone. The MC receptor is expressed in epithelial cells, mainly in the distal nephrons, and also in the gastrointestinal tract.⁶ MCs act by binding to the MC receptor increasing the epithelial sodium channel, extracellular volume, and blood pressure.⁶ These factors might contribute to the mechanisms suppressing diarrhea.

Considering that the GC effects were not confirmed as expected, we further tested the IgE-dependent triphasic cutaneous reaction and contact hypersensitivity models to evaluate their anti-inflammatory genomic effects and confirmed them to be effective (Figure S5). In these models, hydrocortisone exerted the strongest effect to suppress ear swelling, suggesting the association of the MC effect again.

This study had several limitations. First, although randomized, the subjects were not equally assigned to each group. Moreover, the target sample size was not reached. However, all endpoints showed

TABLE 1 Clinical outcomes of the intention-to-treat set

	Prednisolone- (n = 64)	Prednisolone+ (n = 33)	p
Worsening scores	0 (0–75)	0 (0–80)	0.61
Any worsening	26 (40.6%)	16 (48.5%)	0.84
Worsening ≥10 points	18 (28.1%)	10 (30.3%)	0.82
Additional medication use	11 (17.2%)	3 (9.1%)	0.37
Intramuscular adrenaline use	2 (3.1%)	2 (6.1%)	0.60

Note: Data are presented as number or median, and percentage or range. P values were calculated using the Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Worsening of symptoms was assessed by calculating the Anaphylaxis Scoring Aichi.

	Prednisolone- (n = 63)	Prednisolone+ (n = 30)	p
Worsening scores	0 (0–75)	0 (0–80)	0.53
Any worsening	26 (41.3%)	15 (50.0%)	0.51
Worsening ≥ 10 points	18 (28.6%)	10 (33.3%)	1
Additional medication use	11 (17.5%)	3 (10.0%)	0.54
Intramuscular adrenaline use	2 (3.2%)	2 (6.7%)	0.59

Note: Data are presented as number or median, and percentage or range. P values were calculated using the Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Worsening of symptoms was assessed by calculating the Anaphylaxis Scoring Aichi.

TABLE 2 Clinical outcomes of the per-protocol set

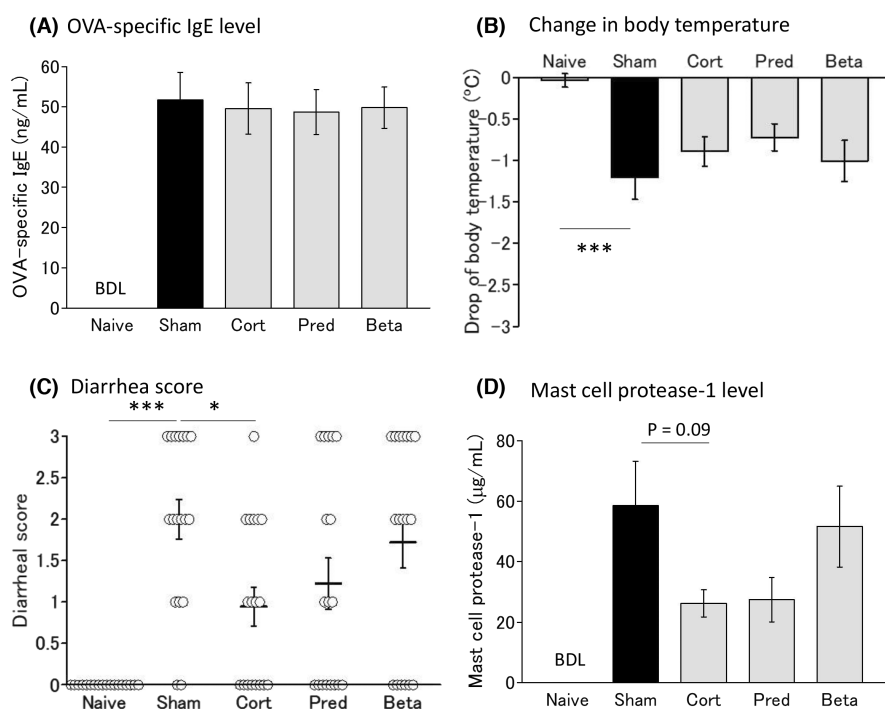


FIGURE 1 Murine food allergy model for glucocorticoid evaluation. Mice were sensitized by the intraperitoneal injections of ovalbumin (OVA) or phosphate-buffered solution with alum adjuvant. Mice were challenged with 50 mg of OVA. Hydrocortisone (Cort), prednisolone (Pred), betamethasone (Beta), or vehicle (Sham) was administered right before the challenge. The OVA-specific IgE was adjusted among the sham and glucocorticoid-treated groups before the challenge (A). Anaphylaxis was evaluated by a decrease in body temperature (B), diarrhea score (C), and mast cell protease-1 level (D). Each value represents the mean $\pm$ SEM of 18 mice. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ versus sham. BDL means below the detection limit.

no clear differences. Moreover, if the exacerbation rate was 10% and 40% in the prednisolone+ and prednisolone- groups, respectively, the statistical power was 0.88, suggesting that GC has no significant preventive effect. Second, antihistamines were used along with prednisolone from an ethical standpoint in the RCT. Third, specific IgEs for wheat differed between groups, which could affect the results.

In conclusion, GCs have no robust rapid effects to protect from exacerbation of FA symptoms.

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KEYWORDS

anaphylaxis, food hypersensitivity, glucocorticoid, prednisolone, steroid

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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