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An injectable excipient prevents anti-polyethylene glycol antibody mediated hypersensitivity

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To the Editor,

Hypersensitivity to polyethylene glycol (PEG) is on the rise.^{1, 2} Sporadic allergy to Covid-19 vaccines have been reported and are suspected to be PEG-related.³ So far, conventional premedication using anti-histamine, steroids, NSAIDs, and leukotriene receptor antagonists are not effective in preventing allergy.⁴

Reactions to PEG are molecular weight (MW) dependent.¹ High MW (HMW, ≥ 1 kDa) PEGs are more likely to trigger reactions than low MW (LMW) PEGs. We investigated the effectiveness of preventive administration of LMW PEG as a decoy to prevent hypersensitivity to HMW PEG mediated by anti-PEG antibodies. Monomeric ethylene and diethylene glycol can inhibit histamine release in an *ex vivo* HMW PEG allergy model.² However, these compounds are too toxic to use *in vivo*. Fortunately, PEG of MW 300–600 Da are safe additives for intravenous injection. Herein, we tested the effectiveness of non-toxic LMW PEG in preventing reactions to HMW PEG mediated by anti-PEG antibodies in a mouse model, using PEG 400 Da as the candidate LMW PEG and PEGylated asparaginase (pegaspargase, PEG MW = 5 kDa) as the cause of HMW PEG hypersensitivity.

To induce anti-PEG antibodies, female Balb/c mice were sensitized with PEG-catalase (prepared with adjuvant); mice sensitized with adjuvant alone served as negative controls (Fig 1A). Sensitization with PEG-catalase successfully induced high levels of anti-PEG

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antibodies ($P = 6.2 \times 10^{-5}$, negative control vs. PEG-catalase sensitized, supplemental Fig 1A). PEG-catalase sensitized mice were further assigned to one of the three challenge regimens (Fig 1A, treatment groups 2–4). Negative control mice were further challenged with pegaspargase (Fig 1A, treatment group 1). Temperature drop measured longitudinally at the center of the head (black cross in Fig 1C&E) using an infrared camera was the indicator for hypersensitivity. Pre-challenge baseline temperature and appearance of PEG-catalase sensitized vs. negative control mice were not different ($P = 0.37$ for temperature). Sensitized mice challenged with pegaspargase (pegaspargase group) had clear allergic reactions, becoming scruffy, less active, and displaying about a 5°C temperature decrease within 30 min after challenge (Fig 1 D&E, red line in Fig 2A). Serum mMCP-1 and IgE were not informative for allergy (Supplemental Methods and Results). Negative control mice stayed groomed and active with no temperature drop from baseline ($P \geq 0.73$ between all post-challenge time points and baseline, Fig 1B&C, gold line in Fig 2A).

PEG-catalase sensitized mice administered PEG 400Da either alone or as pretreatment had similar pre-challenge antibody levels to the pegaspargase group ($P = 0.94$ and 0.72 for PEG 400Da and PEG 400Da + pegaspargase vs. pegaspargase, Fig 2B). PEG 400Da alone did not induce hypersensitivity ($P \geq 0.49$, temperature of PEG 400 (blue line) vs. negative control (gold line) at all post-challenge time points, Fig 2A). When sensitized mice were pre-treated with PEG 400Da and then challenged with pegaspargase, no change in their temperature was observed ($P \geq 0.92$, temperature of PEG 400Da + pegaspargase (green line) vs. negative control (gold line) at all post-challenge time points, Fig 2A), indicating successful prevention of hypersensitivity. These mice also remained active and alert. Temperature AUC of PEG 400 and PEG + pegaspargase mice did not differ from negative control mice ($P = 0.95$ and 0.99 for PEG 400Da and PEG 400Da + pegaspargase vs. negative control, Fig 2C), while the AUC of pegaspargase group was significantly lower than the rest ($P = 3.0 \times 10^{-7}$, Fig 2C). Asparaginase activity was below the detection limit in the pegaspargase group. Although PEG 400Da prevented anti-PEG antibody-mediated pegaspargase hypersensitivity, it did not rescue pegaspargase from increased clearance mediated by anti-PEG antibody ($P = 0.94$, Fig 2D). Pathologic examination of PEG 400Da treated mice did not find signs of toxicity except for microgranulomas at the injection site, which is not considered a safety issue.⁵

We established an anti-PEG mediated HMW PEG hypersensitivity model using noninvasive infrared imaging with no anesthesia needed. Pre-treatment using LMW PEG as an immune decoy prevented hypersensitivity mediated by HMW PEG-conjugated therapeutics. Additional study of this strategy could include consideration of the amount of anti-PEG antibodies in humans, other measures of allergy mediators and antibody subclasses, and the PEG load in different drugs, including those in Covid-19 vaccines made by Pfizer-BioNTech and Moderna.

Reactions to other excipients, such as polysorbates, might also be of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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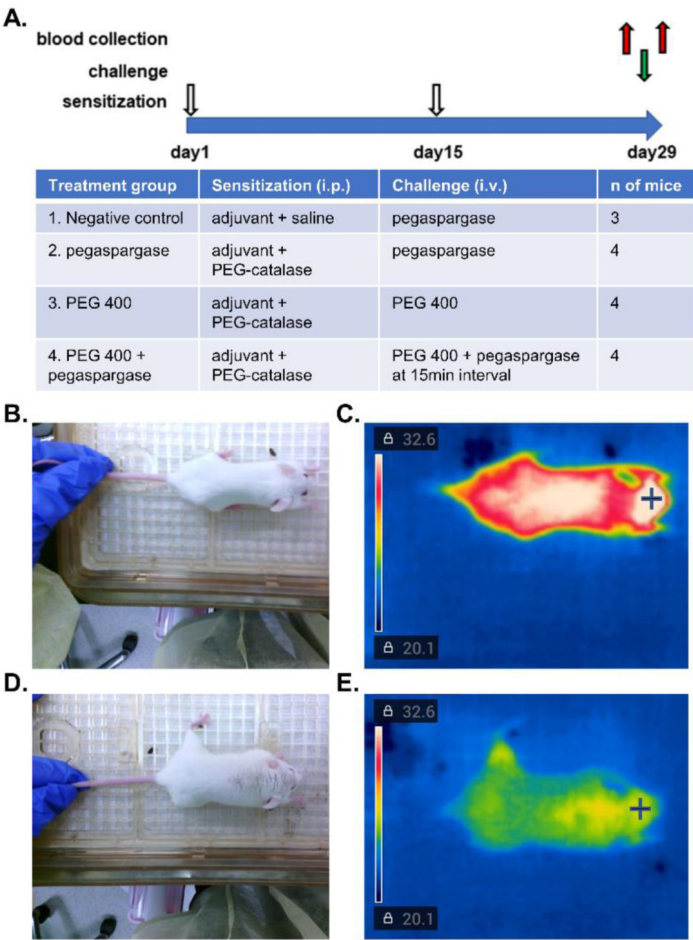


FIGURE 1. Mouse model for anti-PEG antibody-mediated HMW PEG hypersensitivity reactions. Alum was used as adjuvant. Blood was collected one day before challenge for anti-PEG antibody measurement and 2 hours post-challenge for pegaspargase activity measurement. **A**, treatment regimen and groups; **B-E**, Mouse temperature monitoring with infrared imaging; **B-C**, negative control mouse; **D-E**, Mouse sensitized with PEG-catalase and challenged with pegaspargase.

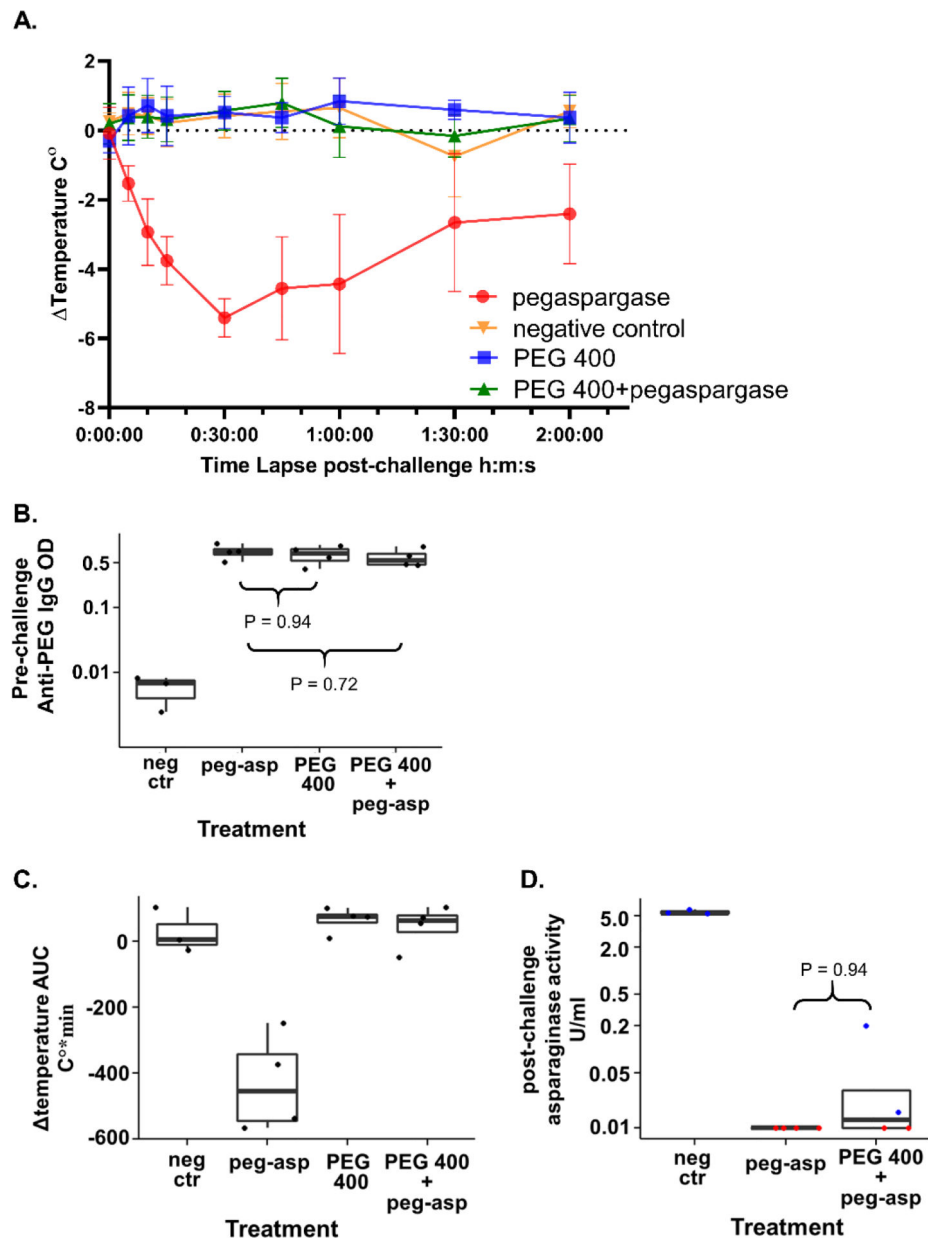


Figure 2.

Prevention of HMW PEG hypersensitivity reactions with PEG 400Da. **A**, Temperature change in different treatment groups up to 120 min post-challenge; **B**, Pre-challenge anti-PEG IgG antibody level in different treatment groups; **C**, Post-challenge 120 min temperature AUC in different treatment groups; **D**, Asparaginase activity 120 min post-challenge in groups challenged with pegaspargase. Red dots indicate measurements below detection limit (0.01U/ml).