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Challenging the norm: Epicutaneous immunotherapy for canine atopic dermatitis

To the Editor,

Allergen immunotherapy (AIT) is a well-established etiological treatment for canine atopic dermatitis (cAD), one of the most prevalent (20–30%),[1] distressing, chronic allergic diseases, accounting for dog's and owner's loss of quality-of-life (QoL).[1]

The remarkable similarities between cAD and its human counterpart create a promising opportunity for reciprocal learning, propelling knowledge, and research from one another.[1,2]

Despite the acknowledged success of conventional subcutaneous AIT for cAD (52–77%),[2] owner compliance is a major challenge in clinical practice.[3] There is, therefore, a need to uncover new AIT modalities and noninvasive, safe, effective, and easy-to-use home-administration routes that promote owner's compliance are warranted.

Although limitedly used in hAD, a recent systematic review of the best evidence has concluded that AIT importantly improves hAD severity and QoL,[4] narrowing the gap between treatment scenarios for both species.

Epicutaneous immunotherapy (EPIT) has recently re-emerged in human medicine as a new promising route of tolerance induction against allergens.[5] The protolerogenic properties of the skin sophisticated immune network underpin EPIT's favourable efficacy and safety profile, linked to patient compliance, even in children and long-term clinical trials.[6] This strategy may also hold promise for cAD.

To our knowledge, this is the first clinical trial addressing EPIT for cAD. Our aims were to assess EPIT's feasibility, effectiveness, and safety in dogs with spontaneous, nonseasonal, mite-sensitive cAD over 6 months and to ascertain owners' adherence to therapy.

This project was approved for ethical standards by institutional committee (016/2020) and owners gave written informed consent for study participation.

Sixteen client-owned dogs were recruited (9 French bulldogs, 7 Labrador retrievers) for a 6-month, once-weekly, 12-h EPIT application (Figure 1). One Labrador retriever was lost to follow-up and all remaining 15 dogs carefully complied with the proposed protocol.

According to the defined success criteria (Data S1), EPIT effectively improved the dogs' clinical condition, with a success rate of 73.3% for pruritus, 66.7% for skin lesions, and 93.3% for QoL (Table S1A–C). Moreover, after both 3- and 6-month EPIT, all dogs had reduced pruritus scores (PVAS10), with a mean improvement of 63% and 56%, respectively. Regarding skin lesions' evaluation, after 6-month EPIT, 9 out of 15 dogs had improved their severity score (2D-IGA) with 57% mean improvement. By the study end, the mean QoL overall improved 58% and 14 out of 15 owners (93.3%) rated the global assessment of treatment efficacy (OGATE) as good-to-excellent, highlighting owners' perceived EPIT benefit.

Although AIT for cAD typically takes 3–9 months to achieve clinical effects, this study shows significant clinical improvement within only one-month EPIT, for both pruritus ($p = .003$) and skin lesions' ($p = .009$) scores (Figure 2), supporting EPIT's potential to induce a rapid clinical response. Over 6 months, mean pruritus, QoL, and skin lesions' scores decreased monthly, reaching significant improvement at the study end (pruritus: $p = .000015$; lesions: $p = .006$; QoL: $p = .000014$) (Figure 2).

EPIT was able to engage the immune system, producing IgE changes already noticeable at 3 months. Partial desensitisation to at least one mite occurred in 40 and 47% of dogs after 3 and 6 months, respectively, while full desensitisation to all mites was achieved by 13% of dogs at both timepoints. Although IgE results did not correlate with clinical improvement, the observed immune modulation suggests EPIT's objective effect.

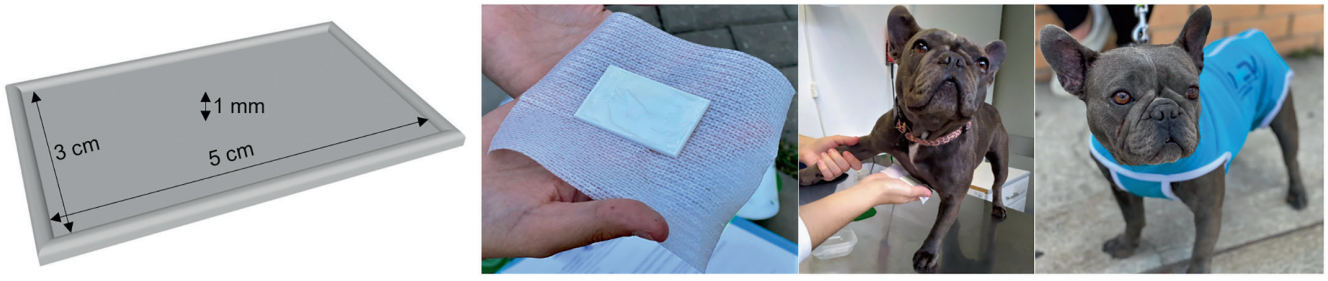

FIGURE 1 3D patch prototype (left) and patch application on an atopic dog (original photos). cm, centimeter; mm, millimeter.

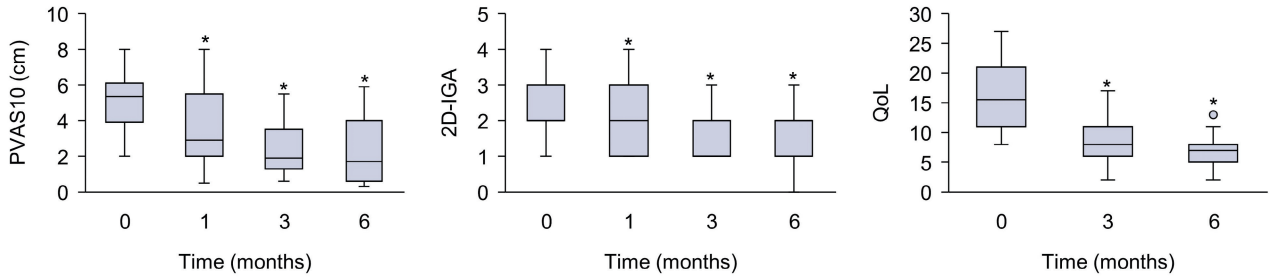

FIGURE 2 Evaluation of pruritus (PVAS10), skin lesions (2D-IGA), and quality-of-life (QoL) throughout the 6 months (boxplots). PVAS10 – Validated owner-assessed 10-cm Pruritus Visual Analog Scale for pruritus evaluation. Scale from 0 ("Normal dog") to 10 ("Extremely severe itching/almost continuous"). Pruritus severity positively correlates with PVAS10 score. 2D-IGA – Validated 2D Investigator's Global Assessment graphic for grading the extent and severity of skin lesions. Scale from 0 ("Clear of skin lesions") to 4 ("Severe skin lesions"). Skin lesions' severity positively correlates with 2D-IGA score. QoL – Quality-of-life survey. Scale from 0 ("Not at all") to 3 ("Very much"). QoL score inversely correlates with dogs' and families' quality-of-life. Significant difference from Month 0 at $^{*}p < .01$, mixed-model ANOVA test.

Adherence to chronic therapeutics is a critical challenge for clinical research, especially for AIT. Nevertheless, we report a 94% adherence rate for EPIT. Additionally, EPIT was practicable, well-tolerated, and safe, with no systemic or severe local reactions. Self-limiting local pruritus was the most common side effect.

This pioneer pilot study emphasises EPIT's potential as a practical and promising, noninvasive, effective, safe, and well-tolerated cAD treatment, supporting further investigation.

AUTHOR CONTRIBUTIONS

Marta Sofia das Neves Pinto: conceptualisation, methodology, patient recruitment, clinical work, writing – original draft, data analysis and interpretation, review and editing. **Solange Judite Roque Coelho Alves Gil:** methodology, supervision, review and editing. **Laura Ramió-Lluch:** conceptualisation, review and editing. **Vanessa Merta Schmidt:** conceptualisation, critical feedback, review and editing. **Hugo Miguel Lino Pereira:** methodology, patient recruitment, clinical work, review and editing. **Beatriz Amaral Pinto Fernandes:** methodology, clinical work, data analysis and interpretation, review and editing. **Ana Filipa Bizarro Camões:** methodology, review and editing. **Mário Morais-Almeida:** conceptualisation, critical feedback, review and editing. **Berta Maria Fernandes Ferreira São Braz:** methodology, review and editing. **Joana Marques Marto:** conceptualisation, methodology, supervision, review and editing. **Ana Mafalda Gonçalves Xavier Félix Lourenço:** conceptualisation, methodology, patient recruitment, supervision, critical feedback, review and editing.

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This research was conducted impartially and no external funding or relationships with organisations that could potentially influence the interpretation of the results were involved in this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Exploring the thaumatin-like protein (TLP) as a candidate cannabis allergen in North-Western Europe

To the Editor,

Cannabis sativa (Can s) can elicit IgE-mediated allergy with a myriad of symptoms.[1-3] Most studies point to Can s 3, the nonspecific lipid transfer protein (nsLTP) as a major allergen.[2] However, Can s 3 does not cover the entire cannabis IgE-reactivity profile.[1]

Earlier research[4] reported patients showing IgE-reactivity to a 38-kDa band, identified as the pathogenesis-related thaumatin-like protein (TLP). The TLP family has been identified as major allergens in several fruits such as kiwi, banana, peach, and apple and is considered a panallergenic family responsible for cross-reactivity between pollen and fruit. Moreover, some TLPs are glycoproteins which could explain their allergenic capacity.[5] However, in the absence of skin testing and functional cellular tests, the authors were unable to comment on the clinical relevance of their observation.[4]

Here we aim to explore the TLP as a candidate Can S allergen in CA in a North-western European region.

Patients with a history of immediate respiratory and/or cutaneous symptoms on cannabis exposure (CA), asymptomatic atopic cannabis users (henceforth designated as exposed atopic controls (EAC)) and asymptomatic exposed healthy controls (EHC) were included as described previously.[1] Total IgE and specific (s)IgE to hemp and recombinant (r) pollen components were quantified by ImmunoCAP (Thermo Fisher Scientific) as described elsewhere.[1] Results were considered positive if ≥0.10 kU_A/L. To depict sensitization to cannabis TLP, sera were analyzed for IgE-reactivity towards rCan s-TLP (rCs-TLP) by using ELISA as described in the Online Repository. The recombinant protein synthesis is detailed in the Online Repository. Figure E1 of the online repository displays rCs-TLP by SDS-PAGE. Finally, rTLP sIgE effector cell activating capacity was evaluated by