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Targeting eosinophils by active vaccination against interleukin-5 reduces basophil counts in horses with insect bite hypersensitivity in the 2nd year of vaccination

Inaugural-Dissertation

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vorgelegt von

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Tierärztin
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Inhaltsverzeichnis

Zusammenfassung

Zur Behandlung von Sommerekzem (IBH), einer saisonal wiederkehrenden allergischen Dermatitis bei Pferden wurden Impfungen mit virusähnlichen Partikeln (VLP), die auf Interleukin (IL)-5 oder IL-31 abzielen, verwendet. Der gegen IL-5 gerichtete Pferdeimpfstoff reduzierte die Anzahl der Eosinophilen im Blut von Pferden signifikant, ähnlich wie menschliche monoklonale Antikörper, die gegen IL-5 oder den IL-5-Rezeptor alpha (IL-5Rα) gerichtet sind. Frühere Studien am Menschen haben auch eine zusätzliche Wirkung auf die Verringerung der Basophilenzahl berichtet. Ziel der vorliegenden Studie war es zu untersuchen, ob ein Anti-IL-5-Impfstoff für Pferde die Basophilenzahl im Blut beeinflusst. Pferde mit IBH wurden in einer 3-jährigen Studie beobachtet. Im ersten Jahr wurde ein Placebo verabreicht, gefolgt von einer Impfung mit einem equinen (e)IL-5-VLP-Impfstoff im zweiten und dritten Jahr. Nach der Impfung gegen IL-5 kam es zu einem starken Rückgang der zirkulierenden Eosinophilenzahlen. Auch die Zahl der Basophilen ging zurück, allerdings erst im dritten Jahr der Studie, was auf einen Nebeneffekt des Anti-IL-5-Impfstoffs auf die Zahl der Basophilen hindeutet.
Schlüsselwörter: Allergie, Basophile, Eosinophile, equines Interleukin-5

Summary

Previously, virus-like particle (VLP)-based self-vaccinations targeting interleukin (IL)-5 or IL-31 have been suggested to treat equine insect bite hypersensitivity (IBH), a seasonal recurrent allergic dermatitis in horses. The IL-5-targeting equine vaccine significantly reduced blood eosinophil counts in horses, similar to human monoclonal antibodies targeting IL-5 or the IL-5 receptor alpha (IL-5Rα). Previous studies in humans have also reported an additional effect on reduction of basophil counts. The aim of the present study was to evaluate whether an equine anti-IL-5 vaccine affected blood basophil counts. Horses with IBH were followed in a 3-year trial consisting of a placebo administered in the 1st year, followed by vaccination using an equine (e)IL-5-VLP vaccine in the 2nd and 3rd years. There was a strong reduction in circulating eosinophil counts after vaccination against IL-5. Additionally, there were reduced basophil counts, but only in the 3rd year of the study, suggesting a bystander effect of the anti-IL-5 vaccine on basophil counts.
Key words: Allergy, Basophils, Eosinophils, Equine Interleukin-5

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Targeting eosinophils by active vaccination against interleukin-5 reduces basophil counts in horses with insect bite hypersensitivity in the 2nd year of vaccination

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ABSTRACT

Previously, virus-like particle (VLP)-based self-vaccinations targeting interleukin (IL)-5 or IL-31 have been suggested to treat equine insect bite hypersensitivity (IBH), a seasonal recurrent allergic dermatitis in horses. The IL-5-targeting equine vaccine significantly reduced blood eosinophil counts in horses, similar to human monoclonal antibodies targeting IL-5 or the IL-5 receptor alpha (IL-5Rα). Previous studies in humans have also reported an additional effect on reduction of basophil counts. The aim of the present study was to evaluate whether an equine anti-IL-5 vaccine affected blood basophil counts. Horses with IBH were followed in a 3-year trial consisting of a placebo administered in the 1st year, followed by vaccination using an equine (e)IL-5-VLP vaccine in the 2nd and 3rd years. There was a strong reduction in circulating eosinophil counts after vaccination against IL-5. Additionally, there were reduced basophil counts, but only in the 3rd year of the study, suggesting a bystander effect of the anti-IL-5 vaccine on basophil counts.

Basophils represent a peripheral circulating population of cells critically involved in allergic responses and share many features and functions with tissue mast cells (Stone et al., 2010). Basophils and mast cells are involved in allergic reactions across species, including humans and horses (van der Haegen et al., 2001; Wagner et al., 2006; Metcalfe et al., 2016). They release histamines and other mediators after IgεRI cross-linking by allergen-specific IgE. To date, various reports have also described a crucial role for IgE, peripheral basophils and mast cells in insect bite hypersensitivity (IBH, or culicoides hypersensitivity [CH]) in horses (van der Haegen et al., 2001; Wagner et al., 2006; Raza et al., 2021). Nevertheless, eosinophils and Th2 cells are the most prevalent cell types found in IBH skin lesions (McKelvie et al., 1999; Schaffartzik et al., 2012). Hence, the virus-like particle (VLP)-based equine (e) IL-5-CuMV$_{TT}$ vaccine, which induces anti-self interleukin (IL)-5 antibodies and thereby reduces eosinophil counts, has been shown to significantly reduce IBH lesion scores throughout the IBH season (Fettelschoss-Gabriel et al., 2018; Wu et al., 2018; Fettelschoss-Gabriel et al., 2019).

Similarly, the human analogue monoclonal antibodies targeting the human IL-5-axis effectively treated eosinophilic allergic human asthma by reducing eosinophil counts in blood and sputum (Leckie et al., 2000; Kips et al., 2003; Haldar et al., 2009; Nair et al., 2009; Ghassemian et al., 2021). Currently, three human monoclonal antibodies are licensed, mepolizumab (GlaxoSmithKline) and reslizumab (Teva Pharmaceuticals), which target IL-5, and benralizumab (AstraZeneca), which targets IL-5Rα. In various studies using benralizumab in non-human primates and in human patients with uncontrolled asthma or eosinophilic asthma, substantial reductions were observed in circulating eosinophil and basophil counts (Kolbeck et al., 2010; Eck et al., 2014; Lommatzsch et al., 2020). This bystander effect was only apparent when the antibody targeting the receptor was used, and did not occur when antibodies targeting the cytokine were used. The mechanism of action is not completely understood, but cell depletion via antibody dependent cell-mediated cytotoxicity (ADCC) has been suggested. As with eosinophils, basophils constitutively express IL-5Rα, but their survival is not dependent on IL-5 (Ochensberger et al., 1999; Yoshimura-Uchiyama

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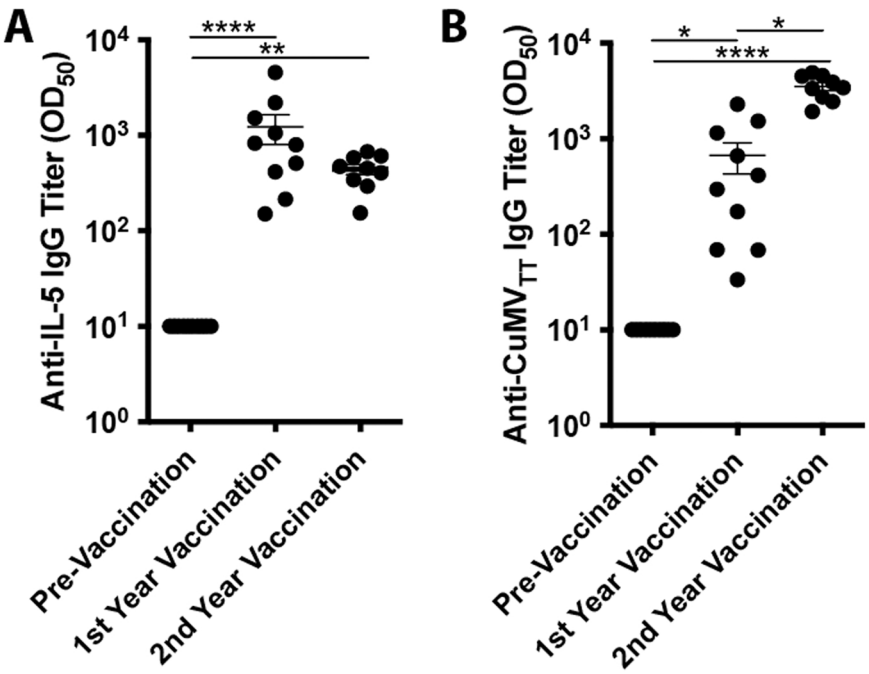

Fig. 1. Antibody titers in vaccinated horses with insect bite hypersensitivity (IBH). Antibody titers in serum are shown as mean per month with months connected by lines, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$. (A) Mean anti- interleukin (IL)-5 antibody titers in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study; (B) Mean anti-CuMV-TT antibody titers in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study.

et al., 2003). Nevertheless, removal of IL-5 might be an alternative explanation for the bystander reduction of circulating basophils.

To evaluate an equine anti-IL-5 vaccine in horses with IBH, eosinophil and basophil counts in peripheral blood were monitored throughout 3 years. In the 1st year, a placebo was administered ($n = 13$), and in the following 2 years, eIL-5-CuMV$_{TT}$ vaccine was administered (Year 1, $n = 13$; Year 2, $n = 11$). Blood was collected from horses at 4-week intervals from April until October each year, with two blood collections in June. All horses were located in their respective stables in Switzerland throughout the study. Blood was collected within the same week for each monthly time point. A total of 7 mL blood was drawn at each collection: 3 mL into EDTA tubes for differential cell counts (IDEXX Diavet), and 4 mL into serum tubes for determination of anti-IL-5 and anti-CuMV$_{TT}$ antibody titers. Figs. 1 and 2 show antibody titers and cell counts as means per month, with months are connected by lines. Antibody titers were measured by ELISA as described earlier (Fettelschoss-Gabriel et al., 2019). Statistical analysis was performed using Kruskal-Wallis tests with correction for multiple comparisons. All experimental procedures were approved by the required cantonal veterinary authorities (Approval number 25152 from 01 January 2014; Approval number 27530 from 11 May 2016; and Approval number 29968 from 28 September 2018).

The 2nd year of the study consisted of three eIL-5-CuMV$_{TT}$ injections: prior to the onset of clinical signs, horses were vaccinated in weeks 0 (February), 4 (March), and 16 (June). In the 3rd year of the study, a single booster injection was administered in March. Anti-IL-5 antibody titers (Fig. 1A; data previously published in Fettelschoss-Gabriel et al., 2019) and anti-CuMV$_{TT}$ antibody titers (Fig. 1B; data previously published in Fettelschoss-Gabriel et al., 2019) increased as expected, i.e. 4 weeks after the 2nd injection in the 2nd year of the study, or 4 weeks after the single booster in the 3rd year of the study (Fettelschoss-Gabriel et al., 2019). As previously reported, eosinophil counts decreased during the 2nd and 3rd years of the study when compared to the 1st year of the study, when a placebo was administered (Fig. 2A; Table 1; data previously published in Fettelschoss-Gabriel et al., 2019). Circulating basophil counts also decreased during the 3rd year of the study (Fig. 2B, Table 1), whereas total leucocyte counts did not change (Fig. 2C). Similarly, no change in monocyte counts were observed (Fig. 2D), but blood monocyte counts followed eosinophil counts throughout the season in the 1st year of the study (Fig. 2E, Table 1).

This study demonstrated decreased circulating basophil counts after anti-IL-5 vaccine administration in horses. While circulating basophils play an important role in allergic reactions, therapy targeting IL-5 may offer broader protection because of its off-target and asynchronous bystander effect on basophils. This is the first report of this phenomenon in horses, and has previously only been reported in humans treated with benralizumab, a monoclonal antibody treatment targeting IL-5Rα. The mechanism by which direct anti-IL-5 treatment results in reduced activity of IL-5 or eosinophil counts, and interferes with basophil counts, is unknown. Nevertheless, a parallel but asynchronous reduction in eosinophils and basophils in response to long-term anti-IL-5 treatment may suggest an indirect role or feedback loop of eosinophils or IL-5 on the regulation of basophils. Remarkably, in another study using the same IL-5 vaccine, comparisons between lesion scores demonstrated significant improvements when results were compared from the 1st year of the study (placebo treatment administered) to the next year (vaccine administered), and from the 1st to the 2nd year of vaccination. Eosinophil counts were reduced to the same extent in both years that vaccine was administered compared to the previous year. However, this was potentially mediated through a reduction in basophil counts in the 2nd year the vaccine was administered (Fettelschoss-Gabriel et al., 2019).

Reducing both eosinophil and basophil counts, two key cell types in allergy, by targeting IL-5, may be a more sustainable and long-term treatment for allergic diseases because of potential additional down-regulation of the IgE-mediated histamine-axis. Thus, long-term anti-IL-5 vaccination administration could result in prolonged improvement in clinical signs of allergy.

In contrast to benralizumab treatment in humans, where eosinophil and basophil depletion occurred simultaneously and immediately, the anti-IL-5 vaccination used in this study immediately reduced eosinophil counts and reduced basophil counts only occurred with long-term treatment, i.e. in the 3rd year of the study. This could suggest two different mechanisms of action. Eosinophils, basophils, and a subset of mast cells are known to express the IL-5Rα (CD125) chain (Wright et al., 2017). Potentially, early eosinophil depletion could be dominated by ADCC, whereas late-stage basophil depletion could occur due to removal of IL-5.

This study demonstrated similar cell count patterns over time for

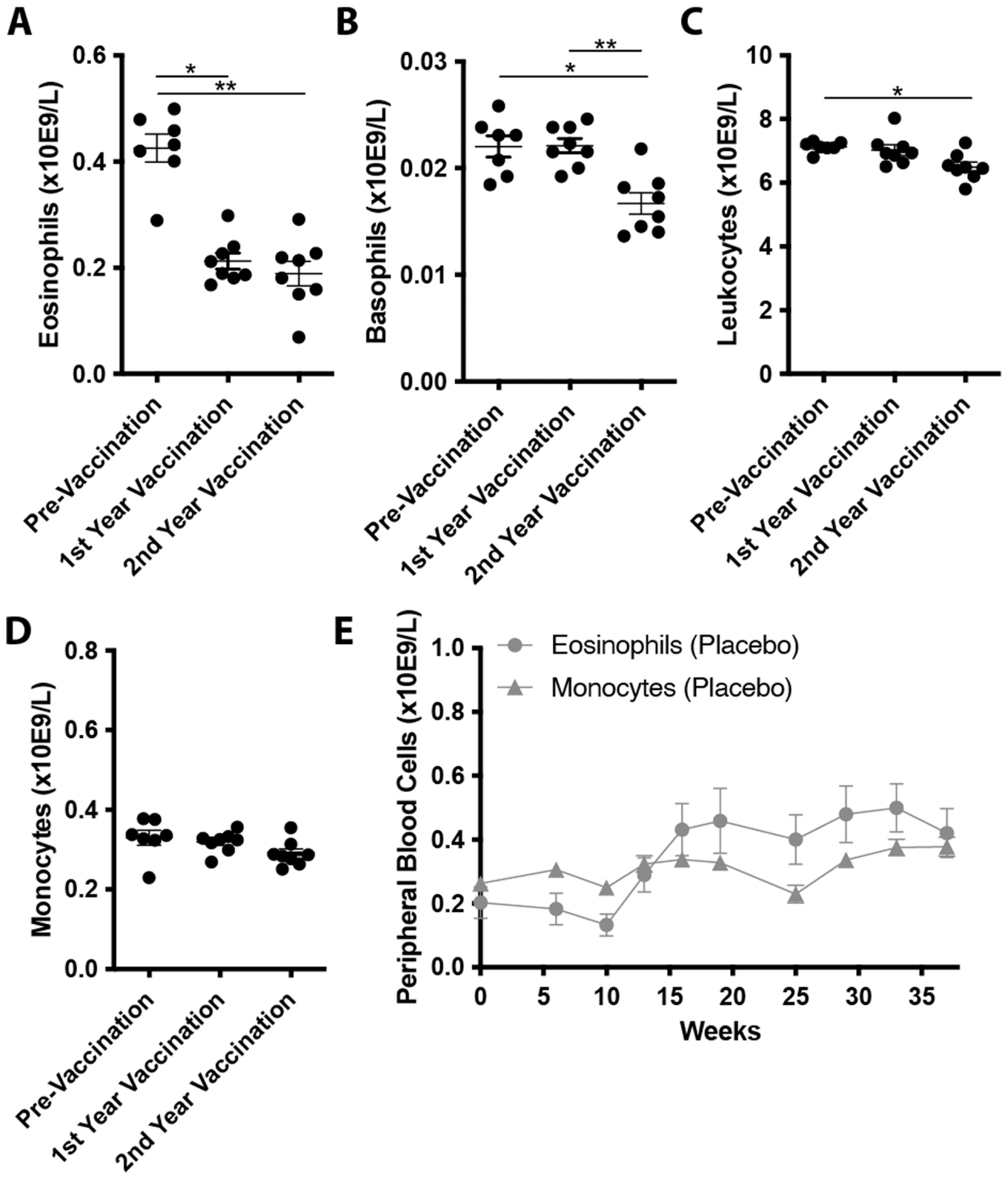

Fig. 2. Circulating cell counts are shown as mean per month with months connected by lines, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$. (A) Mean eosinophil counts in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study; (B) Mean basophil counts in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study; (C) Mean leucocyte counts in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study; (D) Mean monocyte counts in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study; (E) Time course of circulating eosinophils (circles) and monocytes (triangles) during Year 1 of the study (pre-vaccination, placebo-treated), are shown as mean ± standard error of the mean.

Table 1
Mean, standard error of the mean (SEM), and standard deviation (SD) for circulating eosinophil, basophil and monocyte counts from April until October in Year 1 (pre-vaccination, placebo administered), Year 2 (vaccine administered in February, March and June), and Year 3 (single booster vaccination administered in March) of the study.

	April			May			June 1			June 2			July			August			September			October		
Cells ($\times 10^9$/L), year	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD	Mean	SEM	SD
Eos, PRE	0.29	0.19	0.19	0.43	0.28	0.30	0.46	0.35	0.37	ND	ND	ND	0.40	0.27	0.28	0.48	0.27	0.28	0.50	0.26	0.27	0.42	0.27	0.28
Eos, 1ST	0.17	0.29	0.31	0.21	0.28	0.30	0.30	0.33	0.34	0.24	0.55	0.57	0.21	0.34	0.36	0.19	0.39	0.30	0.18	0.25	0.26	0.19	0.28	0.29
Eos, 2ND	0.07	0.09	0.09	0.22	0.31	0.33	0.29	0.36	0.39	0.21	0.31	0.33	0.18	0.23	0.25	0.23	0.28	0.30	0.16	0.18	0.19	0.15	0.14	0.15
Baso, PRE	0.019	0.009	0.010	0.018	0.009	0.010	0.023	0.013	0.013	ND	ND	ND	0.021	0.011	0.011	0.026	0.010	0.011	0.024	0.008	0.009	0.023	0.014	0.014
Baso, 1ST	0.019	0.011	0.011	0.024	0.012	0.013	0.020	0.011	0.012	0.024	0.026	0.027	0.022	0.011	0.012	0.025	0.010	0.011	0.022	0.007	0.007	0.022	0.011	0.011
Baso, 2ND	0.014	0.008	0.008	0.015	0.010	0.010	0.019	0.003	0.004	0.017	0.004	0.005	0.022	0.013	0.014	0.018	0.007	0.008	0.015	0.010	0.010	0.014	0.005	0.005
Mono, PRE	0.32	0.90	0.09	0.34	0.08	0.09	0.35	0.10	0.10	ND	ND	ND	0.25	0.12	0.12	0.35	0.09	0.09	0.35	0.09	0.10	0.39	0.11	0.11
Mono, 1ST	0.30	0.09	0.09	0.36	0.08	0.08	0.34	0.12	0.12	0.29	0.13	0.14	0.31	0.09	0.09	0.33	0.08	0.08	0.33	0.07	0.07	0.33	0.08	0.08
Mono, 2ND	0.27	0.08	0.09	0.26	0.07	0.08	0.30	0.07	0.07	0.28	0.08	0.08	0.34	0.10	0.10	0.30	0.07	0.07	0.30	0.05	0.05	0.36	0.10	0.10

1ST, Year 2 of the study (1st year vaccination was administered); 2ND, Year 3 of the study (2nd year vaccination was administered); Baso, Basophils; Eos, Eosinophils; Mono, Monocytes; ND, Not done; PRE, Pre vaccination year.

monocytes and eosinophils. To our knowledge, this is the first report describing this phenomenon in horses with IBH. This also occurred when horses with IBH received placebo in the 1st year of the study, suggesting that monocytes contribute to the clinical signs of IBH. The exact role of monocytes in the pathogenesis of IBH remains elusive, but monocytes could play a role in IgE binding in horses. In one recent equine study, IgE crosslinking led to IL-8 expression, which had previously been responsible for basophil recruitment (Larson et al., 2020). Our group has reported increased expression of monocyte chemoattracting protein 1 (MCP-1or CCL2) in punch biopsies of non-lesional skin in horses with IBH compared to biopsy specimens of healthy skin from horses without IBH (Olomski et al., 2020). MCP-1 plays a key role in the recruitment of monocytes (Deshmane et al., 2009). Taken together, this points towards a close relationship between eosinophils, basophils and monocytes, potentially mediated by IgE, IL-8 and maybe even IL-5. Further work is necessary for a better understanding of the interplay between those cells.

In summary, in this study, active anti-IL-5 vaccination targeting eosinophils reduced circulating eosinophil and basophil counts in horses with IBH; basophil count only decreased in the 2nd year the vaccine was administered. This may explain the further reduction in clinical signs in the 2nd year that vaccine was administered. Vaccination might result in a sustainable and substantial long-term bystander effect when used to treat the multifactorial allergic signs of IBH. Furthermore, our results suggest that eosinophil and monocyte counts could potentially be linked to the clinical signs of IBH, based on parallel circulating cell counts throughout an IBH season when affected horses received placebo. Both observations, however, require further research, especially regarding their mechanism of action.

Conflict of interest statement

Victoria Fettelschoss, Katharina Birkmann, and Antonia Fettelschoss-Gabriel are involved in the development of therapeutic equines vaccines. Tanya Rhiner and Angelika Schoster have no financial or personal relationships that could inappropriately influence or bias the content of the paper.

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