



Cetirizine inhibits gender-specific blood cell dynamics upon allergen contact in allergic rhinitis

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ABSTRACT

IgE-mediated inflammatory responses upon allergen contact in allergic rhinitis (AR) are associated with rapid alterations of circulating blood cell numbers detectable in a complete blood count (CBC). Aim of this study was to evaluate whether intake of antihistamines may modulate allergen-induced CBC dynamics in male and female patients.

A total of N = 112 specific allergen challenges were performed in otherwise healthy AR subjects. Seventy-two (n = 72) subjects received placebo and forty (n = 40) received cetirizine (H1-receptor antagonist) per os prior to allergen exposure in a randomized, double-blind trial at the Vienna Challenge Chamber (VCC); a subgroup of twenty-five (n = 25) subjects received cetirizine and placebo on different study days (parallel group). Blood samples and symptom scores were taken at baseline and immediately after 6 h of airway challenge simulating ambient allergen contact.

Female sex was associated with a pronounced circulating monocyte increase (p < .01) and male sex with an eosinophil decrease (p < .05) in the placebo group, but not in cetirizine treated subjects. The significant increase in segmented neutrophils (p < .001) and decrease in circulating erythrocytes (p < .01) upon allergen challenge was less prominent after cetirizine intake in both sexes. A more prominent thrombocyte increase in female subjects (p < .05) was noted upon allergen exposure, regardless of prior cetirizine intake.

Cetirizine inhibited the mobilization of neutrophils, lymphocytes and decline in erythrocyte numbers, but did not affect thrombocyte increase upon allergen challenge. It further diminished gender-specific blood cell dynamics. Overall, as reflected in a simple CBC, cetirizine critically diminished immediate and late innate immune responses subsequent to allergen exposure.

1. Background

Allergic rhinitis (AR) is amongst the most pervasive allergic disorders worldwide, with a progressively increasing prevalence of 25–30% in developed countries [1,2] and sex-specific differences in incidence and allergic co-morbidity [3–6]. It is characterized by local

symptoms including nasal congestion, rhinorrhea, and itching. Even though originally regarded as a disease restricted to the nasal mucosa, the view on AR as a purely local phenomenon has been corrected by a growing body of scientific evidence for systemic effects triggered by allergen exposure. Fatigue, mood changes and somnolence, are known to affect mental performance and quality of life in AR patients [7,8]. A

Abbreviations: AIT, allergen-specific immunotherapy; Ant o, *Anthoxanthum odoratum*; AR, allergic rhinitis; CBC, complete blood count; Dac g, *Dactylis glomerata*; DAMP, damage-associated molecular pattern; EDTA, ethylenediamine tetraacetic acid; Hb, hemoglobin; Hc, hematocrit; HDm, house dust mite; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; Lol p, *Lolium perenne*; NF-κB, transcription factor nuclear factor-κB; OA, occupational asthma; OR, occupational rhinitis; Phl p, *Phleum pratense*; RAST, Radio-Allergo-Sorbent-Test; RBC, red blood cell; ROS, reactive oxygen species; SIC, specific inhalation challenge; SPT, skin-prick testing; TNSS, total nasal symptom scores; TOSS, total ocular symptom scores; VCC, Vienna Challenge Chamber

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systematic review of available literature recently illustrated the substantial impairment of work productivity by AR, mostly through presentism, emphasizing its socioeconomic burden [9].

Allergic inflammation in AR involves an extensive set of cytokines and blood cells affiliated with the innate and adaptive immune system. A growing body of research demonstrates that the biological variable 'sex' affects immune functions, probably based on fundamental mechanisms favorable for successful reproduction and survival. This sexual dimorphism in immune responses is mediated by both, sex chromosomes and hormones [10,11]. Several genes involved in the regulation of critical immune responses are encoded on the X chromosome: pattern recognition receptors (TLR7, TLR8), cytokine receptors, transcriptional factors (FoxP3) and molecules e.g. CD40L and CD99, a molecule involved in transendothelial migration of leukocytes [12,13]. While regulatory response genes on the X and Y chromosome can affect sex-dependent dimorphic immune responses, e.g. susceptibility to infection and immune-mediated disease, sex hormone response elements found in the promotor region of these immunity-related genes, suggest that they can be directly modulated by sex hormones [10]. Sex hormones also exhibit effects on functional innate immune cell activity, which subsequently influences adaptive immune responses [14]. Estrogen receptors are expressed on various immune cells, e.g. lymphoid tissue cells, macrophages, lymphocytes, and dendritic cells. Neutrophil recruitment in acute inflammation has been reportedly higher in females, with higher phagocytic activity and higher associated levels of inflammatory markers, such as C-reactive protein [15,16]. Treatment with estradiol also increases blood neutrophil numbers and high estradiol concentrations promote humoral immunity and Th2 immune responses [17]. Androgens, in contrast, can promote anti-inflammatory responses, e.g. by reducing neutrophil leukotriene formation, synthesis of IL10 and transforming growth factor- β [10]. A greater IL10 production in men by peripheral blood mononuclear cells, consisting of monocytes and lymphocytes, with positive correlations to androgen levels has been described [18]. Besides sex-dependent differences in numbers and activity of immune cells, humoral responses are also affected by sexual dimorphism. Women tend to have higher B cell numbers and immunoglobulin levels and manifest greater induction of antibody responses than men. Cytokine responses by immune cells also differ, with e.g. female predominance in IL-13 production [19]. Taken together, the sex-specific regulation of immune responses should also be considered when describing findings in allergic disease [20]. It is an unmet need to understand about sex-dependent differences in blood cell dynamics during allergen challenge in AR.

We have recently reported significant changes in circulating blood cell numbers following allergen exposure in AR patients with seasonal and perennial disease [21,22]. These changes were detectable in a complete blood cell count (CBC), which is a widely available basic diagnostic tool. Comparing blood cell counts taken immediately before to those after several hours of allergen exposure, a rapid mobilization of segmented neutrophils and a significant decline in circulating erythrocytes were noted in otherwise healthy AR subjects. This decrease in red blood cell (RBC) numbers had also been observed in an animal model of allergic airway disease [22]; notably, erythrocyte decline did not occur upon airway challenge with an unspecific antigen or placebo (saline buffer) solution, indicating that the underlying mechanism was indeed associated with allergic inflammation triggered by the specific allergen. This erythrocyte decline and neutrophil increase induced by allergen exposure persisted after successful allergen-specific immune therapy (AIT), as shown in house dust mite (HDM) sensitized AR patients [21]. We concluded that even in AR patients with significant symptom reduction following AIT, the specific allergen still triggers an acute inflammatory response involving erythrocytes and neutrophils in sensitized patients. It remains unclear, however, whether these blood cell dynamics are also observable upon specific allergen contact during active pharmacological symptom control.

Pharmaceutical treatment of AR with antihistamines has been shown to reduce impairment of productivity [23]. Antihistamines, particularly second-generation H₁-antagonists, are established therapeutic options in AR and have been widely investigated regarding clinical efficacy; due to their favorable safety and side-effect profile today they are amongst the most commonly prescribed drugs in the treatment of AR [24]. The symptom-relieving effects of H₁-antagonists are conducted by direct interference with mast cell activation, histamine release and inhibition of histamine effects on small blood vessels and neurons [24]. They further impact antigen presentation by reducing pro-inflammatory cytokine expression, cell adhesion via ICAM-1 and chemotaxis via the transcription factor nuclear factor- κ B (NF- κ B). Amongst the antihistamines prescribed for the treatment of AR at present, cetirizine hydrochloride has been established as particularly efficient and fast-acting, and is thus often used as a standard reference when assessing the effectiveness of new anti-allergic drugs in clinical trials [25]. In a population wide study in Austria we observed that, more women are treated with antihistamines after the age of 20 years [26], which is in accordance with the reported higher prevalence of allergic disease in females after puberty [27]. However, little is known about sex-specific effects of antihistamines on inflammatory responses and blood cell counts, but a recent study revealed that cetirizine reduces clinical side effects of monoclonal antibody therapy directed against CD20+ B cells, in a sex-specific manner [28].

Based on the fast-acting immune-modulating effects of second-generation antihistamines, the aim of the present study was to evaluate whether a basic CBC can still reflect specific allergen contact even under concomitant antihistamine therapy in male and female AR subjects.

2. Materials and methods

2.1. Ethical considerations

All interventions were approved by the ethical committee "Österreichische Arbeitsgemeinschaft für Klinische Pharmakologie" (EK Nr. 04/12; 03/10; EudraCT: 2012-002273-54) before initiation of the study; all participants were exclusively volunteers and only included after gaining written informed consent for study participation. All studies conducted at the Vienna Challenge Chamber are strictly in conformance with GCP (Good Clinical Practice) guidelines.

2.2. Subjects

Healthy adults, except for a history of grass-pollen induced AR, were recruited. Allergen sensitization was confirmed by anamnesis, assessment of elevated specific IgE (≥ 0.7 kU/l, RAST class ≥ 2) and positive skin prick test (allergen wheal ≥ 3 mm compared to control [saline solution]) within 12 months prior to study inclusion. Subjects with anatomical nasal abnormalities (septum perforation, malformations), active respiratory disease or symptoms of acute upper respiratory tract infections within the last 3 weeks and subjects with ongoing potentially immune-modulating medication were excluded. Non-symptomatic subjects with reported mild asthma were included if lung function was normal and if they did not require treatment at time of inclusion.

2.3. Study design

In a randomized, double blind, parallel group clinical drug trial conducted at the VCC, allergen challenge outcomes were assessed in cetirizine and placebo treated patients. Here, forty-one ($n = 41$; "placebo group A") subjects received placebo and forty ($n = 40$; "cetirizine group") received cetirizine per os immediately prior to 6 h of allergen exposure (Supplementary Fig. 1a). To control for baseline blood cell discrepancy depending on time-points of sampling, blood was taken 24 h prior to allergen challenge in thirty-one grass-pollen AR subjects

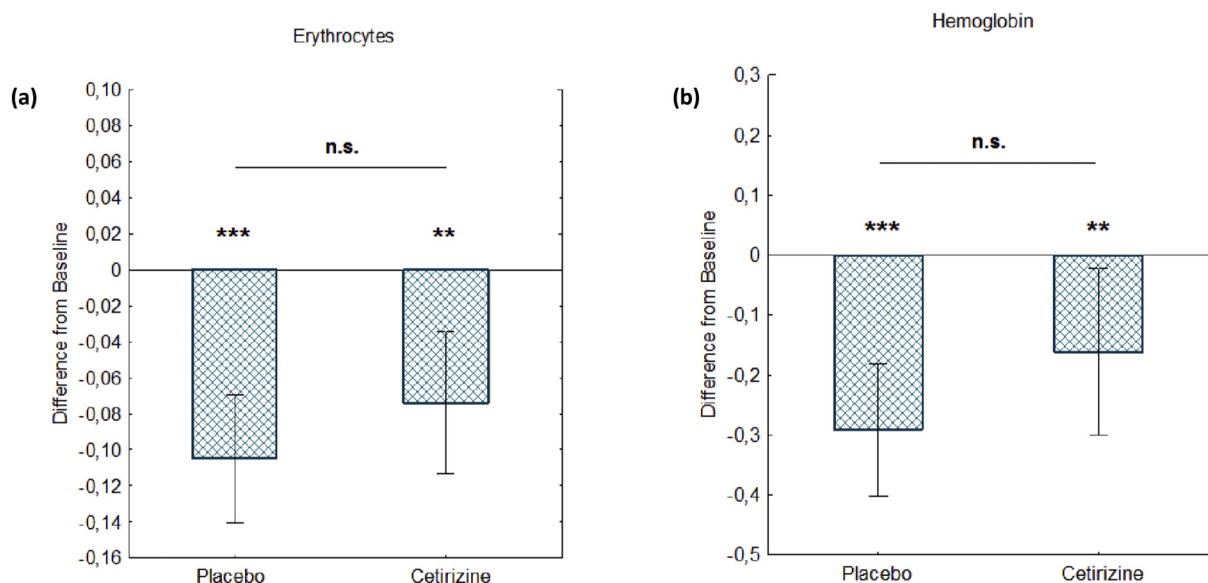


Fig. 1. Changes in circulating erythrocyte numbers and hemoglobin (Hb) values following 6 h of allergen challenge compared to baseline after placebo and cetirizine intake. ** $p < .01$; *** $p < .001$; mean and 95% confidence interval; n.s. ... not significant.

($n = 31$; “placebo group B”; EK Nr. 03/10). (Supplementary Fig. 1b).

2.4. Allergen challenge

Airway allergen exposure was conducted in a specialized approximately 58 m³ large airtight provocation chamber for a total of 6 h consecutively outside of allergen season, as previously described [21]. A pure mixture of Phl p (*Phleum pratense*), Dac g (*Dactylis glomerata*), Lol p (*Lolium perenne*) and Ant o (*Anthoxanthum odoratum*) in equal parts (Allergon, Thermo Fisher Scientific, Ångelholm, Sweden) was constantly dispersed into the chamber via ventilation system; airborne allergen concentration was monitored and kept constant at approximately 1500 pollen/m³ to simulate the daytime burden in allergen season. All pollen allergens were provided with certificates of analysis by the manufacturer and dryly stored at + 2 °C to + 10 °C before application. As previously described, every 15 min allergic symptoms were self-reported by the participants for calculation of total nasal symptom scores (TNSS, i.e. sum of nasal congestion, rhinorrhea, nasal itching and sneezing), total ocular symptom scores (TOSS, i.e. watery, itchy and reddened eyes) and every 30 min nasal secretion was assessed by weighing used tissues and nasal airflow volume was assessed by active anterior rhinomanometry [21,22].

2.5. Blood sampling

Venous blood was collected in ethylenediamine tetraacetic acid (EDTA) coated tubes at baseline (immediately before [$n = 41$, “placebo group A”; and $n = 40$, “cetirizine group”] or 24 h before [$n = 31$, “placebo group B”]) and after 6 h of allergen challenge in all patients (Supplementary Fig. 1). EDTA blood was shortly stored at +2 °C to + 10 °C and analyzed by an ISO 9001-certified lab (Labors.at, Vienna, Austria) for complete and differential blood cell counts, and levels of hematocrit (Hc) and hemoglobin (Hb).

2.6. Statistical analysis

Data was analyzed by sigma-restricted parameterization (ANOVA) with the factors group (placebo or cetirizine), sex as an inter-subject and before/after challenge as an intra-subject factor. Normality of residuals was tested by using Kolmogorov-Smirnov with Lilliefors correction; variances homogeneity was tested by Levene's tests. In all

statistical tests a level of $p < .05$ was considered significant. The software packages SPSS (version 24.0 for Windows, IBM Corp., USA) and STATISTICA (version 12.0; StatSoft Inc., USA) were used for statistical calculations.

3. Results

3.1. Patient characteristics

In total, $N = 112$ allergen challenge sessions (6 h of allergen exposure) were conducted in healthy adults with confirmed grass-pollen AR. A) seventy-two ($n = 72$; 70.8% male; age 30.3 ± 7.7 years) were allergen challenged after placebo; B) forty ($n = 40$; 57.5% male; age 31.05 ± 9.6 years) after cetirizine intake per os; C) a subgroup of twenty-five ($n = 25$) subjects were challenged after placebo and after cetirizine intake on different study days, respectively.

Observations regarding circulating blood cell dynamics in the subgroup of subjects ($n = 25$) challenged on different study days after placebo and cetirizine intake, respectively, did not significantly differ from observed outcomes for the entire study population as described below. Further, time-point of baseline blood sampling, i.e. immediately (“placebo group A”) or 24 h (“placebo group B”) before allergen challenge, had no significant impact on findings after allergen challenge. Hence, both placebo groups (A + B) are further referred to as one (combined) placebo group.

3.2. Effect of allergen challenge on circulating erythrocyte counts

Absolute erythrocyte counts, Hb and Hc values were lower after 6 h of allergen challenge compared to baseline values in the placebo group ($p < .001$, respectively). These findings were slightly less prominent in cetirizine-treated AR subjects ($p < .01$ for RBC and Hc, respectively; and $p < .05$ for Hb), but these differences between both groups did not reach statistical significance. (Fig. 1 a + b) In female subjects, RBC and Hc decrease was less prominent in the placebo group ($p < .05$, respectively) and did not reach statistical significance after cetirizine intake. MCH (mean corpuscular hemoglobin), MCV (mean corpuscular volume) and MCHC (mean corpuscular hemoglobin concentration) values after allergen challenge did not significantly differ from baseline values regardless of drug intake.

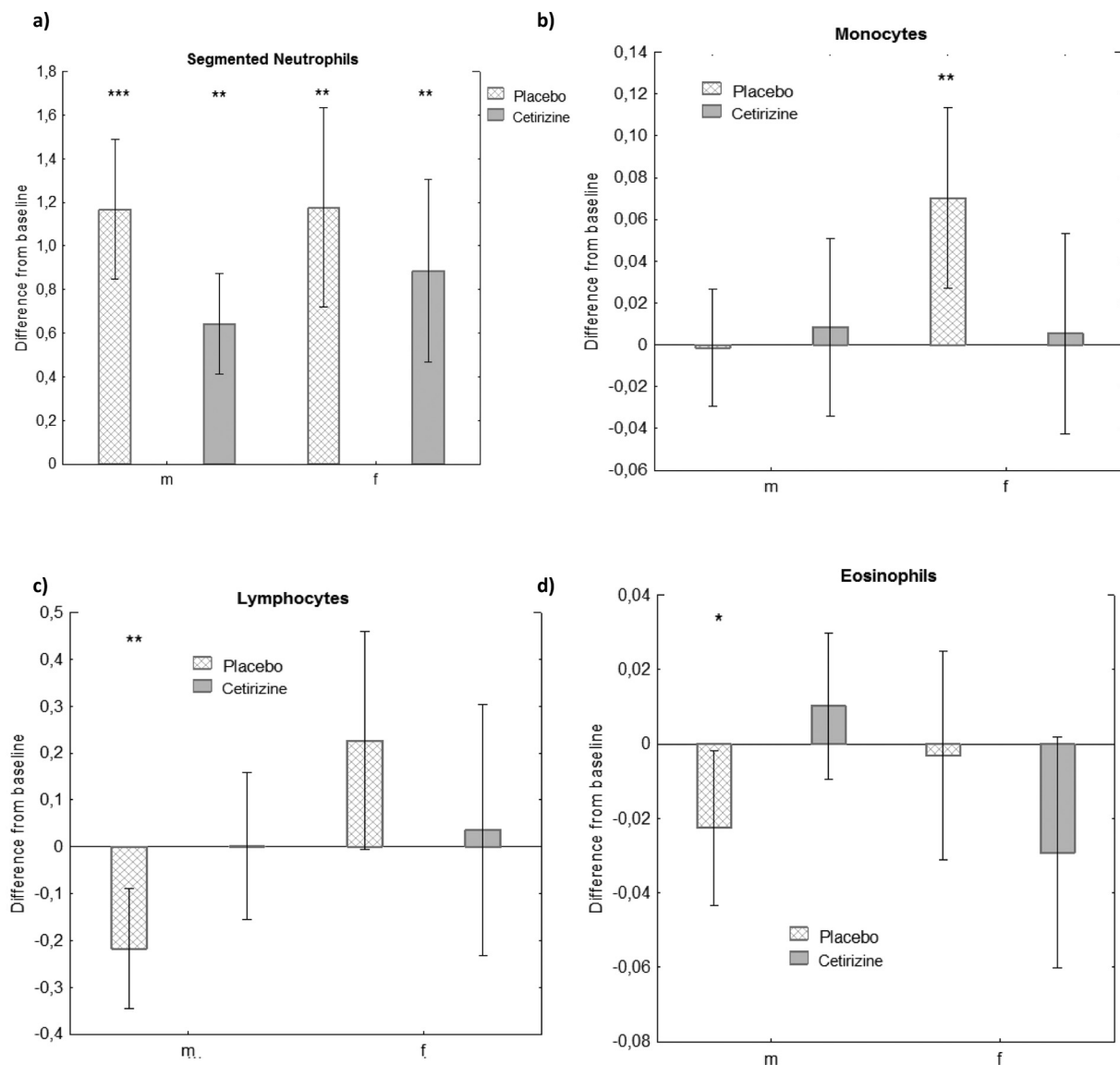


Fig. 2. Changes in absolute (a) segmented neutrophils, (b) monocyte, (c) lymphocyte and (d) eosinophil numbers following 6 h of allergen challenge compared to baseline values in female (f) and male (m) AR subjects after placebo and cetirizine intake, respectively. * $p < .05$; ** $p < .01$; *** $p < .001$; mean and 95% confidence interval.

3.3. Leukocytes

Absolute leukocyte ($p < .001$ in females and $p < .01$ in males in the placebo group; $p < .05$ in females and $p < .01$ in males in the cetirizine group) and segmented neutrophil numbers ($p < .01$ in females and $p < .001$ in males; $p < .01$ in females and males in the cetirizine group, respectively) were significantly higher after 6 h of allergen challenge compared to baseline (Fig. 2a); segmented neutrophil increase was significantly more prominent in the placebo group compared to cetirizine-treated subjects ($p < .05$). These findings were statistically similar for both sexes. An elevation of band neutrophils in female subjects ($p < .05$) was noted in the placebo group only. Regarding other leukocyte subsets, an increase in monocytes, was observed in female AR subjects in the placebo group only ($p < .01$; Fig. 2b). Lymphocyte numbers slightly increased in women ($p = .051$) and, in contrast, significantly decreased in men ($p < .01$) in the placebo group, but remained stable after allergen challenge in cetirizine-treated subjects, regardless of sex (Fig. 2c). A significant decrease in eosinophils numbers after allergen challenge was found in male subjects in the placebo group only ($p < .05$) (Fig. 2d).

No significant differences between the cetirizine group and the placebo group were found regarding changes in other leukocyte subsets, i.e. basophils and band neutrophils, after allergen challenge.

3.4. Thrombocytes

After 6 h of allergen challenge, thrombocytes slightly increased in the cetirizine group and the placebo group ($p < .05$, respectively) (Fig. 3a); no significant differences were found regarding thrombocyte changes in the placebo and the cetirizine group. Thrombocyte increase was generally more prominent in female subjects ($p < .05$), regardless of cetirizine intake (Fig. 3b).

3.5. Clinical symptom scores and correlation with blood cell counts

Analysis of clinical symptom scores after placebo and cetirizine intake showed comparable differences for the subgroup of allergen exposed subjects ($n = 25$) as described for total participant numbers. TNSS were significantly higher during airway allergen challenge in untreated AR subjects (placebo group A) resulting in a symptom

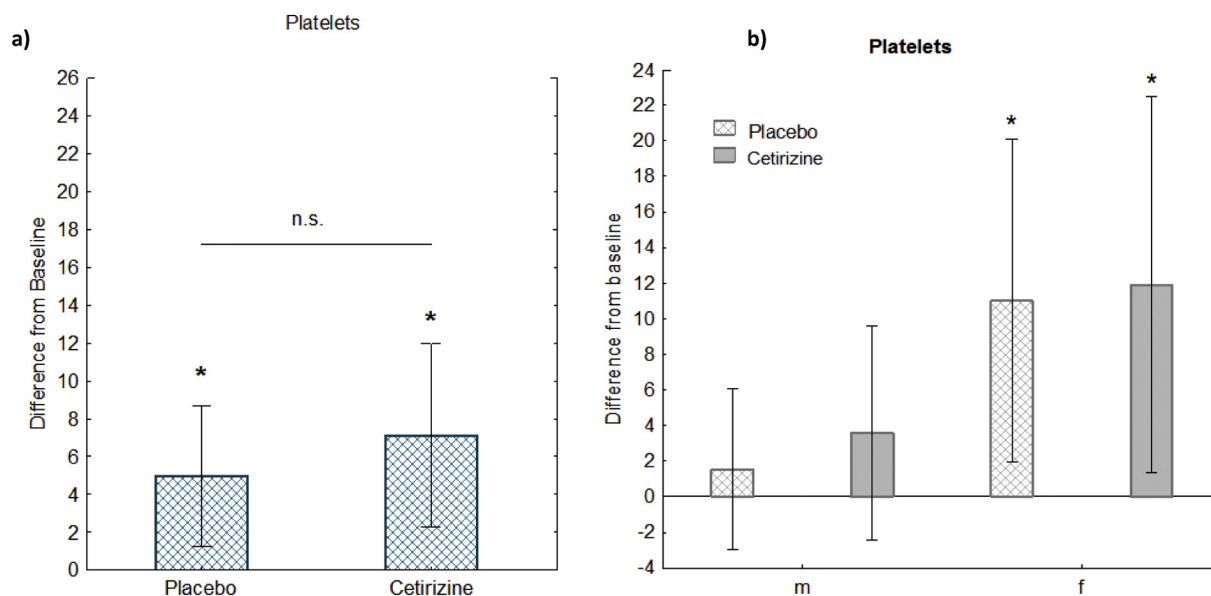


Fig. 3. Changes in thrombocyte numbers following 6 h of allergen challenge compared to baseline values (a) in total and (b) in female (f) and male (m) AR subjects after placebo and cetirizine intake. * $p < .05$; n.s. ... not significant; mean and 95% confidence interval.

reduction of $\approx 30\%$ by cetirizine (4.80 vs 6.87; $p < .001$); additionally, nasal secretion was $\approx 54\%$ lower (0.84 vs 1.83), nasal congestion was 12% lower (1.70 vs 1.93) and nasal air flow volume was similar (26% vs 29%) after cetirizine intake. TOSS during allergen exposure was also significantly lower after cetirizine intake ($p < .01$); compared to female subjects a relatively higher TOSS increase was observed in male subjects after cetirizine and placebo, respectively. TNSS scores correlated with increases in thrombocytes (cetirizine group) and lymphocyte (placebo group) numbers in women only ($p < .05$, respectively). In women, a tendency to report less subjective symptoms (TNSS, TOSS) than men after cetirizine intake compared to placebo was noted; objective outcomes (nasal airflow in rhinomanometry, nasal secretion weight) did not significantly differ between sexes after cetirizine intake. All clinical symptom courses are provided for female and male subjects of the parallel group setting ("cetirizine group" and "placebo group A") in Supplementary Fig. 2.

4. Discussion

Following specific allergen challenge in AR, rapid changes in circulating blood cell numbers, particularly segmented neutrophils and erythrocytes, were observed in a basic CBC compared to baseline values. These findings were diminished in AR subjects under systemic treatment with an H_1 antihistamine, i.e. cetirizine. The anti-inflammatory properties of second generation antihistamines have been demonstrated in numerous studies in seasonal and perennial AR [24,29], significantly reducing inflammatory cells infiltrates, e.g. neutrophils and eosinophils, as well as pro-inflammatory nasal mucosa interleukin levels (IL-4, IL-8) [24,30,31]. As expected, cetirizine intake before allergen challenge resulted in lower symptom scores and favorable clinical outcomes (e.g. TNSS, TOSS, nasal secretion) in our study, but was additionally associated with differences in allergen-induced blood cell dynamics.

A basic CBC describes the main three blood cell types: erythrocytes, leukocytes and thrombocytes. Following allergen challenge, a decline in erythrocytes, i.e. RBC, and accordingly in hematocrit, can already be noted after 4h²² and persists in CBC after 6 h of allergen challenge. In cetirizine-treated AR subjects the decline in red blood values was less prominent. In the subgroup of females, who had received cetirizine before allergen challenge, RBC decline did not reach statistical significance. This is explained by the physiologically lower female baseline

red blood values compared to males, which, despite a proportionally similar erythrocyte decline in female AR subjects, resulted in a lower overall RBC decline in all study groups. The role of RBC in innate inflammatory responses has recently been discussed [32]. While the pathophysiological processes resulting in a red blood decline during allergic inflammation are not yet fully understood, splenic erythrocyte retention and cysteinyl-leukotriene induced eryptosis have been previously proposed as a potential underlying mechanism in allergen challenge [21].

Absolute leukocyte numbers, and particularly segmented neutrophils rapidly increased in circulating blood upon allergen exposure. Compared to baseline values assessed in differential blood count before allergen contact, an increase in segmented neutrophils can already be noted as early as 2 h after allergen contact [22]. While a segmented neutrophil increase upon allergen challenge was generally found in AR subjects regardless of sex, band neutrophils slightly increased in female subjects of the placebo group only, as a sign of premature mobilization from bone marrow. This finding might be impacted by estrogens, as estradiol was shown to enhance granulocyte-macrophage colony-stimulating factor production, which is again associated release of peripheral blood progenitor cells from bone marrow [33]. The elevation in circulating segmented (and band) neutrophils was significantly however diminished in cetirizine-treated subjects regardless of sex. Other leukocyte subsets, however, were also associated with sex-dependent differences: while cetirizine-treated subjects showed no significant changes in blood monocytes regardless of sex, monocytes significantly increased after 6 h of allergen challenge in women only. This finding might be associated with the above described mobilization of band neutrophils in female subjects, as inflammatory signals have recently been shown to induce a phenotypic change, "transdifferentiation" of these immature neutrophils into monocytes [34]. Sex-dependent differences in inflammatory cytokine release and in anti-inflammatory effects of drugs have been described [35]; progesterone was associated with diversity of the local cellular immune response in allergic airway disease [36,37], with a sex hormone specific immune modulation of macrophages [38]. Further, effects of estrogen on molecular macrophage function appear to include a modulation of their responsiveness to Th2 cytokines [39]. In our study, circulating eosinophil numbers were decreased after 6 h of allergen challenge significantly in men only, possibly reflecting different stages in eosinophil recruitment to the airways via circulating blood. Another explanation for this finding

might be an estrogen-associated suppression of eosinophil mobilization [10]. A surface estrogen receptor on circulating eosinophils was further shown to exhibit pro-apoptotic effects on IL-5-stimulated eosinophils [40]. While sexual dimorphism in the allergic immune response clearly links estrogen and eosinophils, data on concrete effects of female sex hormones on eosinophil functions is still emerging.

Interestingly, absolute lymphocyte numbers significantly increased in women but decreased in men after 6 h of allergen exposure in our study. The observed lymphocyte increase in women correlated well with their nasal symptoms. Beside higher numbers of B cells and immunoglobulin levels in women, serum IgE and allergen dose-dependent inflammatory responses have previously been reported as higher in female mice, with a decreased Th2 cell response in males [41]. These findings appear analogous to outcomes in our study. In contrast, lymphocyte numbers remained constant following allergen challenge in cetirizine-treated subjects regardless of sex. As histamine is known to play a critical role in orchestrating recruitment of Th2 cells to the site of allergic airway inflammation via H1R [42], these findings were little surprising. While the approach of our study did not include further analysis of lymphocyte subsets, the relative consistency of total lymphocyte numbers during allergen challenge in cetirizine-treated patients implies a drug induced inhibition of Th2 lymphocyte recruitment.

Allergen challenge also resulted in an increase in circulating thrombocytes in both, the cetirizine and the placebo group. This increase was more prominent in females and even correlated with nasal symptoms in cetirizine-treated women. In contrast, our previous findings in HDM induced AR showed no significant impact of allergen exposure on circulating platelet counts [21]. While platelets appear to have a central role in effector cell recruitment and can promote leukocyte attachment to epithelia [43,44], their precise functions in allergic inflammation are yet to be established.

In summary, we describe specific changes in circulating blood cell counts upon allergen challenge in AR, which are detectable in a widely available CBC. Particularly erythrocytes and segmented neutrophils numbers are rapidly impacted by allergic inflammation, while dynamics of other leukocyte subsets and thrombocytes appeared more variable, probably depending on the phase of allergic inflammation. The RBC and neutrophil dynamics following allergen challenge reported in the current study have been robust throughout our series of studies in seasonal and perennial AR, allowing the conclusion that they are generally associated with the IgE-mediated Th2 response. Our findings were assessed in a setting of ambient allergen exposure, similar to environmental and workplace-related allergen encounter and resulted in significant clinical symptoms, which were controlled by cetirizine intake. The described changes in circulating blood cell numbers were further consistent regardless of baseline blood sampling time-point, i.e. immediately or 24 h prior to allergen challenge. While we did not observe significant sex-specific improvement in objective measures, i.e. rhinomanometry and nasal secretion, a tendency to report a greater improvement of symptoms, e.g. nasal itching or congestion, after cetirizine intake was noted amongst women compared to men. This might be associated with the generally slightly higher symptom reports by women previously attributed to greater inflammatory responses or reporting bias [10], as also seen for nasal symptoms amongst female AR subjects in our placebo group. In contrast to these observations and recent findings of a Korean study, our male subjects generally reported more eye symptoms, as reflected by higher TOSS, when compared to female subjects; a higher prevalence of unreported concomitant allergic (rhino)conjunctivitis amongst our male AR subjects might have to some extent attributed to these findings.

Our study is the first to our knowledge to describe the effect of cetirizine on circulating blood cell counts following allergen challenge in a placebo-controlled manner; however, it has some limitations. Since our focus lay on evaluation of complete and differential blood cell counts as basic diagnostic tool in allergic inflammation, lymphocyte subsets were not further differentiated. The blood lymphocytes

involved in the allergic Th2 response are well researched [21,45]. Further, our findings regarding effect of cetirizine on allergen induced blood cell dynamics were described for systemic intake and might vary for local, i.e. intranasal, antihistamine application, which would need to be evaluated in further studies. These should also consider sex differences in the allergic immune response, in regards to common efforts in the direction of precision medicine.

5. Conclusions

Cetirizine inhibited the observed rapid changes in circulating leukocytes and erythrocyte numbers following allergen exposure, reflecting pharmacological effects of antihistamine on IgE-mediated innate immune responses in AR. Systemic treatment with cetirizine further diminished gender-specific changes in lymphocytes, monocyte and eosinophil dynamics induced upon allergen challenge, which were partially associated with nasal symptoms. Interestingly, cetirizine did not affect the observed increase in circulating thrombocyte numbers during allergen exposure possibly implying alternative mobilization pathways. Overall, a simple blood count can reflect allergen exposure, whereas cetirizine demonstrably dampens inflammation-induced cell recruitment.

Authors' contributions

Galateja Jordakieva: Conceptualization; Investigation; Data Analysis; Data Interpretation; Methodology; Original draft preparation. Michael Kundi: Conceptualization; Statistical Analysis; Visualization; Data Interpretation; Software; Writing- Reviewing and Editing. Patrick Lemell: Data Acquisition; Project administration; Investigation; Resources; Software; Writing - review & editing. Petra Zieglmayer: Data curation; Investigation; Project administration; Resources; Writing - review & editing. René Zieglmayer: Data Acquisition; Supervision; Project administration; Investigation; Resources; Software; Writing - review & editing. Erika Jensen-Jarolim: Conceptualization; Data Interpretation; Formal analysis; Supervision; Writing- Reviewing and Editing. Richard Crevenna: Supervision; Data Interpretation; Writing - review & editing.

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Declaration of Competing Interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clim.2020.108422>.

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