Check for updates

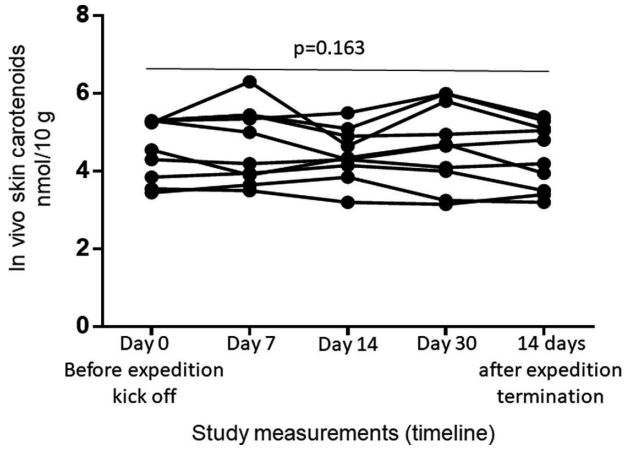


Figure 1 Dynamics of carotenoid levels in the skin of healthy volunteers before, during and after return from the Bulgarian Antarctic expedition 2017. Data expressed in nmol/10 g skin with mean values ± standard deviation.

the lowest value of carotenoid levels during the expedition was detected at day 14, which was similar to the ones registered after return to Europe.

Carotenoids reduce the generation of free radicals by UV light which results in their depletion from the skin upon UV exposure.[1] Therefore, solar exposure in Antarctica would result in a decrease of skin carotenoid levels. On the other hand, healthy lifestyle, diet and physical activity affect the antioxidant defence of the organism and the skin in particular.[6,7] Healthy diet correlates with a high cutaneous antioxidant concentration including carotenoids.[4] Lifestyle during Bulgarian Antarctica expedition includes three times daily eating regime with balanced Balkan diet and unexclusive presence of at least one fresh fruit or vegetable with each meal as well as intensive physical activity (at least and not limited to 15 000 steps/daily).[8] Skin carotenoid dynamics could be an equilibrium between negative factors such as UV radiation, humidity and temperature on the one hand and the beneficial ones, namely healthy lifestyle, diet and physical activity, on the other. A certain limitation of our study is the small number of volunteers that is a subject of future development of skin physiology studies in Antarctica. The practical implication could be the introduction of antioxidant strategies that could improve the skin health of Antarctica expedition members.

Acknowledgements

None.

N. Tsankov,[1,*] D. Mateev,[2] I. Bogdanov,[1] R. Darlenski[1,3]

[1]Department of Dermatology and Venereology, Acibadem Cityclinic Tokuda Hospital, Sofia, Bulgaria, [2]Bulgarian Antarctic Institute, Sofia, Bulgaria, [3]Department of Dermatology and Venereology, Trakia University Stara Zagora, Bulgaria

*Correspondence: N. Tsankov. E-mail: tsankn@abv.bg

References

1 Darvin M, Sterry W, Lademann J, Vergou T. The role of carotenoids in human skin. *Molecules* 2011; **16**: 10491–10506.
2 Darlenski R, Hristakieva E, Aydin U *et al*. Epidermal barrier and oxidative stress parameters improve during in 311nm narrow band UVB phototherapy of plaque type psoriasis. *J Dermatol Sci* 2018; **91**: 28–34.
3 Englund SL, Adams BB. Winter sports dermatology: a review. *Cutis* 2009; **83**: 42–48.
4 Yu RX, Kocher W, Darvin ME *et al*. Spectroscopic biofeedback on cutaneous carotenoids as part of a prevention program could be effective to raise health awareness in adolescents. *J Biophotonics* 2014; **7**: 926–937.
5 Darvin ME, Sandhagen C, Koecher W, Sterry W, Lademann J, Meinke MC. Comparison of two methods for noninvasive determination of carotenoids in human and animal skin: Raman spectroscopy versus reflection spectroscopy. *J Biophotonics* 2012; **5**: 550–558.
6 Meinke MC, Lohan SB, Kocher W, Magnussen B, Darvin ME, Lademann J. Multiple spatially resolved reflection spectroscopy to monitor cutaneous carotenoids during supplementation of fruit and vegetable extracts in vivo. *Skin Res Technol* 2017; **23**: 459–462.
7 DeWeerdt S. The edible skincare diet. *Nature* 2018; **563**: S94–S95.
8 Pimpirev C Davidov N. Antarctica: The Extreme South. St. Kliment Ohridski University Press, Sofia, 2003.

DOI: 10.1111/jdv.16702

The Fcε receptor I pathway is crucial but not exclusive for basophil activation in patients with autoimmune forms of chronic spontaneous urticaria

To the editor

Ibrutinib, an irreversible and specific Bruton's tyrosine kinase (BTK) inhibitor, leads to complete inhibition of IgE/FcεRI-BTK degranulation of human basophils without affecting the signalling via G protein-coupled receptors (C5a, fMLP).[1,2] Since autoantibodies in chronic spontaneous urticaria (CSU) either against the IgE/FcεRI complex or IgE play a relevant role in CSU,[3,4] ibrutinib could, therefore, be a promising asset in basophil assays.[5] This *in vitro* study aimed to differentiate between FcεRI-dependent and FcεRI-independent pathways in autoimmune CSU (aiCSU).

Serum from patients with aiCSU (total n = 24, age range 24–71 years, 62.5% female) was investigated in two basophil assays with donor basophils (CU-BAT) according to the literature[6,7]; either with releaser basophils of six well-characterized healthy donors under ibrutinib inhibition (phase 1, n = 20/24) or with non-releaser basophils of two healthy donors, unresponsive to

© 2020 European Academy of Dermatology and Venereology

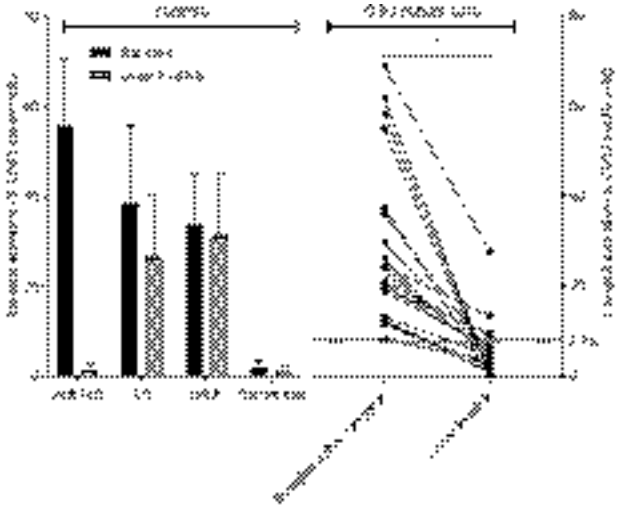


Figure 1 Phase 1: Releaser basophils of well-characterized donors primed with optimal IL-3 concentration with and without pretreatment of ibrutinib (100 nmol/L for 15 min) were incubated with the serum of patients with chronic spontaneous urticaria (CSU), n = 20/24. Values represent the measurement of CD63, expressed as the percentage of activated basophils (*CD63 %: 29.1% ± 18.2 vs. 5.1% ± 6.4, $P < 0.0001$). 7.7% was defined as the cut-off of basophil activation for study inclusion. Anti-IgE, C5a, *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) and serum mix of six healthy donors were used as controls.

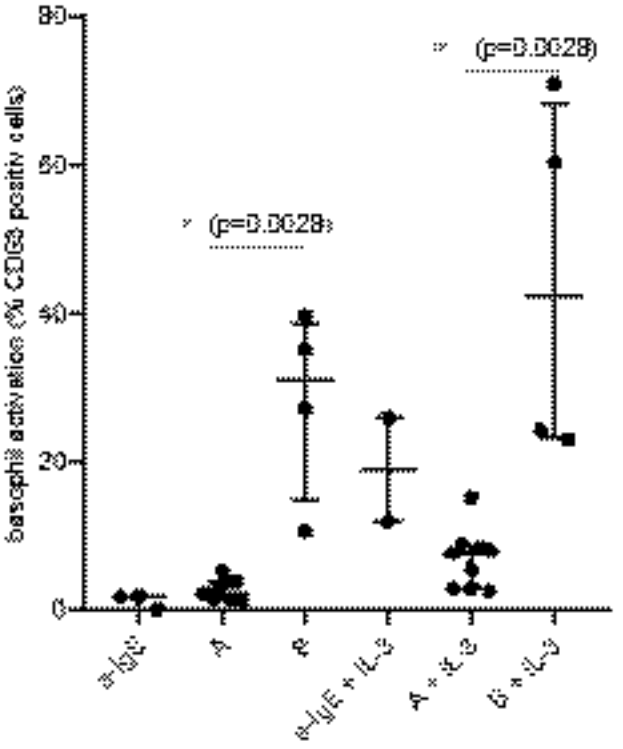


Figure 2 Phase 2: Evaluation of non-releaser donor basophils (unresponsive to FcεRI stimulation without priming) stimulated with the serum of CSU patients (n = 13/24). Group A represents CSU sera not active on non-releaser basophils, in contrast to group B whose sera activate non-releaser basophils without the addition of IL-3 primer. All experiments with non-releaser basophils were done with and without IL-3 priming. Anti-IgE served as a control. Values represent the measurement of CD63 up-regulation, expressed as the percentage of activated basophils (%).

FcεRI stimulation without IL-3 priming (phase 2, n = 13/24). In nine out of 24 cases, both experiments were performed. Anti-IgE (100 ng/mL; Beckman Coulter, Marseille, France), C5a (Sigma-Aldrich, St. Louis, MO, USA) and fMLP (Sigma-Aldrich) served as positive and a serum mix of healthy donors (n = 5) as a negative control. CD63 served as an activation marker and was expressed as the percentage of activated basophils. Only serum samples with a CD63 up-regulation of at least 7.7% at baseline in CU-BAT were evaluated, to only include aiCSU.

Ibrutinib experiments (phase 1, n = 20/24): Compared to baseline, the percentage of activated donor basophils after stimulation with patient serum was significantly reduced under ibrutinib (CD63 29.1% ± 18.2 vs. 5.1% ± 6.4, $P < 0.0001$): a complete inhibition could be observed in 16 of 20 patients. Interestingly, four out of 20 patients' sera could partially activate donor basophils despite ibrutinib inhibition (Fig. 1). Non-releaser experiments (phase 2, n = 13/24): When using non-releaser basophils without IL-3 priming, nine out of 13 aiCSU patients' sera were not able to stimulate unprimed basophils (Fig. 2, subgroup A). In contrast, the sera of four patients led to significant CD63 up-regulation of non-releaser basophils (2.8 ± 1.4% vs. 28.1 ± 12.8%, P = 0.0028). Even after priming with IL-3, CD63 expression was significantly higher in the subgroup B (6.9 ± 4.0% vs. 44.6 ± 24.6%, P = 0.0028). Importantly, serum IL-3 levels in aiCSU sera were low and below the level required for priming. A comparison of both experiments showed that sera of two patients who were only partially suppressed by ibrutinib in CU-BAT could not activate non-releaser basophils. Interestingly, the serum samples of two cases with complete ibrutinib inhibition were able to activate non-releaser basophils without IL-3 priming, a circumstance already observed by MacGlashan.[5]

There are limitations of our in vitro study: since our study was conducted in two phases, not all patient sera were subjected to both experiments, which make it difficult to find a correlation between the two effects. Especially in the assays with non-releaser basophils, the number of participating patients was low.

In summary, this in vitro study shows that the IgE/FcεRI-BTK pathway seems to be dominant for the degranulation of basophils treated with aiCSU sera, but its inhibition does not completely abrogate basophil activation in all patients. Incomplete inhibition in four aiCSU serum samples by ibrutinib and the

 © 2020 European Academy of Dermatology and Venereology

ability of four sera to elicit activation in non-releaser basophils suggest that in some aiCSU, sera pathways or factors beyond or in addition to FcεRI triggering of basophils may exist. It seems that the serum of some aiCSU patients contains a factor ('second signal') that may act as a basophil primer, enhancing signalling through FcεRI and inducing CD63 up-regulation. The exact nature of factors outside the IgE/FcεRI-BTK signalling remains still unclear and will be the focus of future studies.

Conflicts of interest

WJP and OH are employees of ADR-AC GmbH, a specialized laboratory offering basophil activation tests for routine diagnostics in Switzerland.

Funding source

Ulrich Mueller-Gierok Allergy Foundation, Bern.

Ethics approval and consent to participate

This study was approved by the local ethics committee (Kantonale Ethikkommission Bern). All patients included in this study gave informed consent.

L. Jörg,[1,*,†] N. Mueller-Wirth,[2,†] T. Pecaric-Petkovic,[2] C. Diaz,[2] W. Pichler,[2] O. Hausmann[2,3]

[1]Department of Rheumatology, Immunology and Allergology, Inselspital, Bern University Hospital,University of Bern, Bern, Switzerland, [2]ADR-AC GmbH,Adverse Drug Reactions, Analysis and Consulting, Bern, Switzerland, [3]Löwenpraxis Luzern, Lucerne, Switzerland

*Correspondence: L. Jörg. E-mail: lukas.joerg@insel.ch

[†]Contributed equally

References

1 Smiljkovic D, Blatt K, Stefanzl G *et al*. BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. *Allergy* 2017; **72**: 1666–1676.

2 MacGlashan D, Honigberg LA, Smith A, Buggy J, Schroeder JT. Inhibition of IgE-mediated secretion from human basophils with a highly selective Bruton's tyrosine kinase, Btk, inhibitor. *Int Immunopharmacol* 2011; **11**: 475–479.

3 Soundararajan S, Kikuchi Y, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005; **115**: 815–821.

4 Schoepke N, Asero R, Ellrich A *et al*. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST Study. *Allergy* 2019; **74**: 2427–2436.

5 MacGlashan D. Autoantibodies to IgE and FcεRI and the natural variability of spleen tyrosine kinase expression in basophils. *J Allergy Clin Immunol* 2019; **143**: 1100–1107.

6 Gentinetta T, Pecaric-Petkovic T, Wan D *et al*. Individual IL-3 priming is crucial for consistent in vitro activation of donor basophils in patients with chronic urticaria. *J Allergy Clin Immunol* 2011; **128**: 1227–1234.

7 Jörg L, Pecaric-Petkovic T, Reichenbach S *et al*. Double-blind placebo-controlled trial of the effect of omalizumab on basophils in chronic urticaria patients. *Clin Exp Allergy* 2018; **48**: 196–204.

DOI: 10.1111/jdv.16703

What counts? The relationship between patient estimated numbers of painful hidradenitis suppurativa lesions over 4 weeks compared with clinician's lesion count at the time of examination

Dear editor,

Hidradenitis suppurativa (HS) is a chronic disease where recurrent painful nodules, abscesses and/or tunnels/sinus tracts develop in inverse regions of the skin.[1] Clinical assessment and patient experience is used to monitor disease severity and progression during treatment. However, clinical assessment is not standardized and can be challenging.[2]

The HS cORe outcomes set International Collaboration (HISTORIC), an international multi-stakeholder and collaborative patient/physician driven group has proposed a universal core outcome set for HS clinical trials,[3–5] and a specific HS quality of life questionnaire has been validated.[6] Both constitute important endeavors as prior inadequately validated outcome measures have made meta-analysis and other systematic data extraction difficult.

To investigate the degree of mutual correlation between patient and physician-based outcome measures, specifically patients' self-evaluated number of painful boils/nodules and number of lesions found during clinical examination we conducted a retrograde cohort register study. The lesion count of all patients treated for HS at our department was compared to the number of painful boils experienced by the patient during the last 4 weeks (PB4W). The correlation was first assessed via Bland–Altman plot and then a multiple linear regression adjusting for the effects of sex, age, pain, BMI, smoking, disease duration and severity was conducted. Data were obtained from the Register for HS (HiSReg) database, a Scandinavian clinical quality HS database established to assess the safety and effectiveness of different treatments.[7]

Descriptive statistics of the 342 unique Danish HiSReg patients is presented in Table 1. Participants were around 40 years old, three quarters were female, their median BMI was 30.7, 54.7% smoked and 26.6% had stopped. Their median age of onset and at diagnosis was 18, and 28 years, respectively.

Patients averagely reported their PB4W as 4.2/4.7 (89%) the number of lesions found during physical examination (Table 1). While this association is very good, the disagreement increased with the number of lesion uncovered by the physicians. Thus while agreement was high for all with five or fewer lesions, more than a third with seven or more lesions varied at least two

 © 2020 European Academy of Dermatology and Venereology