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Subject: EAACI – Allergopharma Award, Final Report

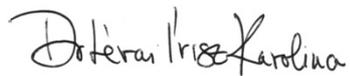
Dear Professor Schmid-Grendelmeier (EAACI Vice President Education & Specialty),

I am very honoured and grateful to have received the EAACI-Allergopharma Award in 2016.

Thank you so much for this recognition and giving me the opportunity to expand my knowledge base and enhance my research skills in an excellent host centre.

As requested, please find below the final report of the project.

Yours sincerely,

A handwritten signature in black ink that reads "Dr. Iriz Karolina". The signature is written in a cursive style with a large initial 'D'.

Irisz Karolina Levai, MD

Continuous laryngoscopy during exercise and assessment of parasympathetic activity in patients with exercise-induced laryngeal obstruction (EILO)

As an EAACI - Allergopharma Awardee, I had the privilege to spend 6 months at Haukeland University Hospital (HUS) in Bergen (Norway), the leading centre in Europe for continuous laryngoscopy exercise (CLE) testing to undertake a project looking at the effect of Atrovent on exercise-induced laryngeal obstruction (EILO).

The Host Unit, Haukeland University Hospital (HUS) provides effective and high quality health care as well as conducts and facilitates exceptional clinical and translational research. HUS functions as a national reference centre for patients complaining of exercise induced inspiratory symptoms (EIS), receiving approximately 100 new patients every year and performing 5-10 CLE tests every week. In the last 13 years, the EILO research group has performed over 1000 successful CLE tests and developed a specific CLE score system, which enabled them to become the world experts in the area. The host supervisor, Professor Thomas Halvorsen has co-authored over 30 publications related to laryngeal dysfunction and has over 15 years' clinical research experience in this field. He is the head of the ERS Task Force group on inducible laryngeal obstructions, which has recently set the new taxonomical standards for this condition.

Exertional breathlessness and wheeze represent the most common respiratory symptoms encountered in adolescents and young adults [1-2]. The differential diagnosis for these symptoms is broad [3]; however, asthma is often diagnosed despite limited objective supporting evidence. A key reason for this is the failure to accurately identify conditions that 'mimic' asthma. [4] One such condition, termed exercise-induced laryngeal obstruction (EILO), arises from the development of temporary laryngeal narrowing on exercise, limiting airflow. In a recent study, EILO was found to be as prevalent as asthma in young individuals referred with unexplained breathlessness, and many were receiving inappropriate treatment [5-6]. The causative mechanisms of this condition have not yet been clarified and currently all attempts on treatment are empirical and based exclusively on subjective reports.

The gold standard means for diagnosing EILO is via a specialist test termed the continuous laryngoscopy during exercise (CLE). [7] This technique combines a full cardio-respiratory

treadmill exercise set-up and uses flexible naso-endoscopy to provide a continuous image recording of the larynx throughout an exercise to the maximum, thereby enabling a dynamic recording of the movement of the laryngeal structures from start to stop. The uninterrupted nature of this recording is important, given the fact that symptoms may rapidly abate on exercise cessation and thus be undetected if only assessed before and after a challenge. It also permits characterisation of the anatomical location of the obstruction, which is recognised to have treatment implications that may be important for planning surgical intervention. CLE testing is currently only available in a very few centres in the world and yet improved access is important in order to enable improved clinical diagnosis to help patients, but also to aid an expansion of research in the field.

Inducible laryngeal obstructions were previously often labelled vocal cord dysfunction (VCD). Ayres et al. [8] previously proposed that VCD could be a function of an altered autonomic balance. This view opened for a theoretical framework for treatment of VCD using inhaled anticholinergic agents such as Ipratropium bromide (Atrovent®). To our knowledge, positive effects from inhaled anticholinergic agents in VCD have so far only been published as case reports, and systematic studies have not been performed.

The autonomic nervous system (ANS) controls the function of internal organs such as the heart and the lungs but also regulates bodily functions such as the pupillary response. Pupillometry is a valid and low-cost method for the evaluation of autonomic nervous system activity that has a potential to allow an independent evaluation of both types of an ANS activity. [9] Experimental studies have shown that the vagal control of heart rate (HR) plays an important cardioprotective role during exercise. The heart rate is widely used as a target organ of parasympathetic activity; heart rate variability (HRV) reflects the continuous oscillation of the R-R intervals around its mean value, providing a non-invasive method to evaluate the autonomic regulation of heart rate. [10]

The present study therefore aimed to address potential effects from Atrovent in patients with EILO and to evaluate the presence of autonomic dysfunction in these individuals. Specifically, the primary endpoint was a significant improvement in the subjective evaluation of the overall symptoms experienced during exercise by the patients, rated on the visual analog scale (VAS). The secondary endpoint of the study was two-folds: (1) a significant improvement in distance ran during a cardio-pulmonary exercise test, and (2) improvement in

the degree of the laryngeal obstruction seen objectively through laryngoscopy during increasing airflow velocity induced by increasing exercise intensity.

Four out of the 51 patients, who were referred to the outpatient clinic of Haukeland University Hospital for exercise-induced inspiratory symptoms (EIS) and diagnosed with EILO during a routine CLE test during the fellowship period, fulfilled the test criteria and completed the study. Patients attended the test laboratory on two separate occasions and underwent the following assessments (with and without prior treatment with Atrovent): pupillometry, heart rate variability measurements, spirometry and CLE test.

Preliminary results of this study suggest that the use of Atrovent had no significant effect on any of the studied parameters. Specifically, following Atrovent administration, we found no improvement in (1) the subjective evaluation of the overall symptoms and exercise dyspnoea rated by the patients using the VAS and Borg-10 scales, respectively, (2) the distance ran during the CLE test or (3) the degree of the laryngeal obstruction observed with laryngoscopy and evaluated objectively using CLE scoring. Results however should be interpreted with caution due to the low number of patients participated in the study. Amendment of the inclusion criteria would be necessary in order to recruit an adequate number of patients and to draw a firm conclusion of the findings.

Further research may focus on classifying the underlying mechanisms of EILO, as well as identifying and determining optimal and individualised evidence-based treatment strategies, in which clinical experience and individual clinical signs are integrated with the best available research information.

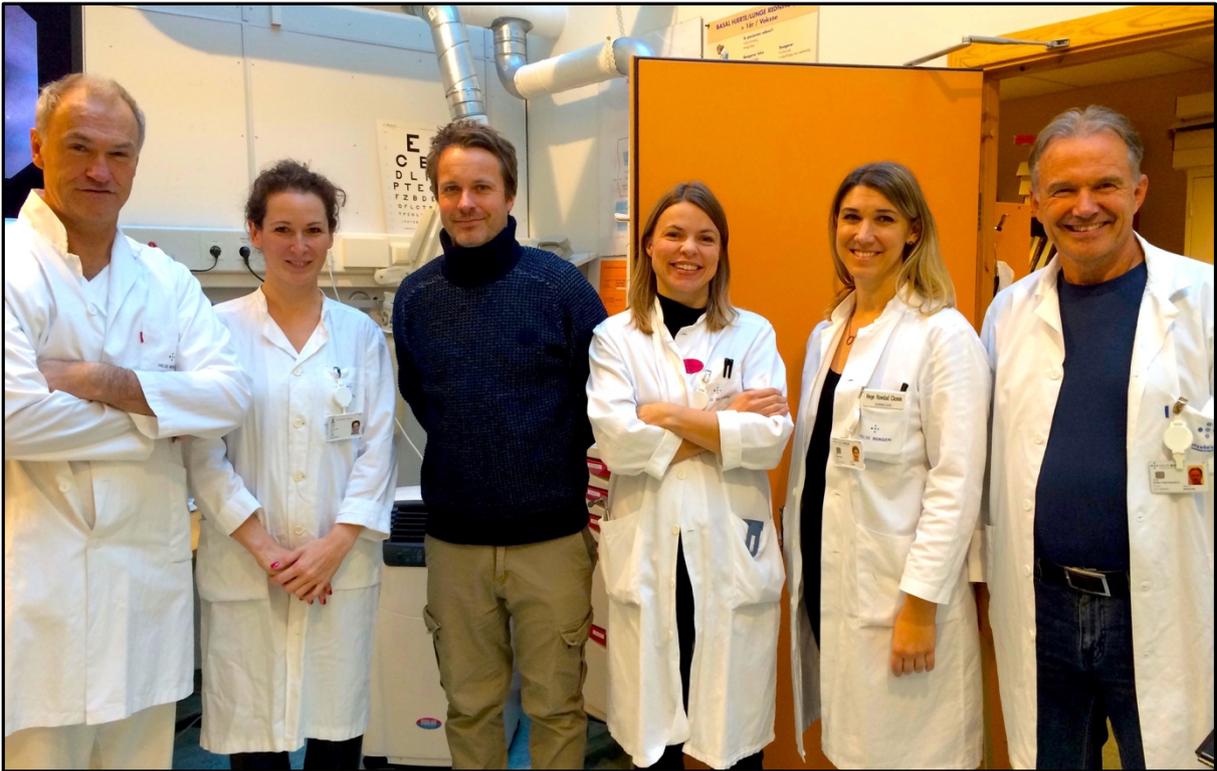
The clinical techniques I learnt during the fellowship greatly complimented my research experience in areas aligned to but outside of my existing research strengths and by doing so I developed a unique set of skills for addressing exercise-respiratory issues in a diverse population. Additionally, the fellowship has broadened my professional network and provided the basis for developing future career projects in existing and newly established international collaborations.

I am very pleased and honoured to have won the EAACI-Allergopharma Research Award in 2016. I am grateful to EAACI and Allergopharma, who made the award possible, this

recognition has encouraged and enhanced my research abilities and helped me contribute something substantial to the field of respiratory medicine. I extend my sincere gratitude and appreciation to Professor Thomas Halvorsen and his research group for this initiative and for the warm welcome and all the support I have received.

References:

- [1] Hull, J.H., Ansley, L., Robson-Ansley, P. and Parsons, J.P., 2012. Managing respiratory problems in athletes. *Clinical Medicine*, 12(4), pp.351-356.
- [2] Price, O.J., Ansley, L., Menzies-Gow, A., Cullinan, P. and Hull, J.H., 2013. Airway dysfunction in elite athletes—an occupational lung disease? *Allergy*, 68(11), pp.1343-1352.
- [3] Røksund, O.D., Maat, R.C., Heimdal, J.H., Olofsson, J., Skadberg, B.T. and Halvorsen, T., 2009. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respiratory medicine*, 103(12), pp.1911-1918.
- [4] Weinberger, M. and Abu-Hasan, M., 2007. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*, 120(4), pp.855-864.
- [5] Johansson, H., Norlander, K., Berglund, L., Janson, C., Malinovschi, A., Nordvall, L., Nordang, L. and Emtner, M., 2014. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax*, pp.thoraxjnl-2014.
- [6] Dickinson, J., McConnell, A. and Whyte, G., 2011. Diagnosis of exercise-induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. *British journal of sports medicine*, 45(14), pp.1126-1131.
- [7] Christensen, P.M., Heimdal, J.H., Christopher, K.L., Bucca, C., Cantarella, G., Friedrich, G., Halvorsen, T., Herth, F., Jung, H., Morris, M.J. and Remale, M., 2015. ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions. *European Respiratory Review*, 24(137), pp.445-450.
- [8] Ayres, J.G. and Gabbott, P.L.A., 2002. Vocal cord dysfunction and laryngeal hyperresponsiveness: a function of altered autonomic balance?
- [9] Kaltsatou, A., Kouidi, E., Fotiou, D. and Deligiannis, P., 2011. The use of pupillometry in the assessment of cardiac autonomic function in elite different type trained athletes. *European journal of applied physiology*, 111(9), pp.2079-2087.
- [10] Camm, A.J., Malik, M., Bigger, J.T., Breithardt, G., Cerutti, S., Cohen, R.J., Coumel, P., Fallen, E.L., Kennedy, H.L., Kleiger, R.E. and Lombardi, F., 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*, 93(5), pp.1043-1065.



The EILO research group at Haukeland University Hospital in Bergen (Norway)
From the left: Prof Thomas Halvorsen, Dr Irisz Karolina Levai, Dr Magnus Hilland,
Dr Maria Vollsæter, Dr Hege Clemm and Dr Ola Røksund



Continuous laryngoscopy exercise (CLE) testing at Haukeland University Hospital