

Non-histaminergic Angioedema Patients: Identification, Characterization and Treatment (NAPICAT)

A thesis on angiotensin converting enzyme-inhibitor induced angioedema

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Eva Rye Rasmussen defended her PhD thesis “Non-histaminergic Angioedema Patients: Identification, Characterization And Treatment (NAPICAT)” the 28th of September 2018. Professor Teresa Caballero and Dr. Ulrich Strassen served as opponents. Associate Professor Claus Rikard Johnsen acted as chair of the assessment committee. Main supervisor was Professor Christian von Buchwald, Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Denmark. Co-supervisors were Professor Anette Bygum, Professor Preben Homøe and Professor Mia Wadelius.

Angioedema is a non-pitting swelling of skin and mucosa, and can be a symptom of several diseases. It also occurs as an adverse reaction to treatment with angiotensin-converting enzyme-inhibitors (ACEi). The incidence of this adverse reaction has increased significantly over the past decade, and can become life-threatening if located in the airways. With this PhD study we wanted to investigate the epidemiology, pharmacogenetics and adverse reaction report pattern. Furthermore we wanted to clarify whether patients with prior angioedema due to ACEi treatment can safely be treated with angiotensin receptor blockers.

Paper I describes the analysis of 105 patients diagnosed with ACEi angioedema. This was an observational retrospective cohort-study performed between 1995 and 2014. Being female was associated with a higher risk of angioedema. More than half of the patients had been hospitalized due to angioedema. Five patients needed acute airway management. The risk of admission was highest if angioedema was located in the head/neck area. The most used international classification of diseases version 10 code for ACEi angioedema was T78.3 Quincke's oedema.

Paper II describes a case-control analysis based on a genome-wide association study (GWAS) performed on 175 angioedema patients and 4,890 population controls. In addition a comparison was made with 1,345 treated controls. The GWAS identified one gene, *KCNMA1*, associated with ACEi angioedema. We then pursued to replicate the findings in a separate cohort using genotyping. The variants showed a trend towards a positive association, but did not reach statistical significance.

In paper III we used patient data from papers I and II that linked all ACEi angioedema patients' Central Person Registry numbers to the Danish Adverse Drug Reaction Database. This enabled us to calculate that the ADR report rate was



1%. Enalapril was the drug most commonly associated with angioedema in our cohorts and in the Danish Adverse Drug Reaction Database.

Paper IV reports the results of a registry-based study that used the Danish National Patient Registry to extract data for all ACEi angioedema patients over a 23-year period. Patients were then followed up to assess their subsequent use of antihypertensive drugs and their risk of recurrent angioedema. In total 5,507 cases of ACEi-AE were identified. There was no increased risk of angioedema in patients subsequently treated with angiotensin receptor blockers (hazard risk 0.39). Therefore, there is no reason to avoid using angiotensin receptor blockers to treat patients with prior ACEi angioedema.

In conclusion, female sex and older age predispose for ACEi angioedema. In our GWAS one gene was found to be associated to ACEi angioedema. This adverse reaction is massively underreported to the Danish adverse drug reaction database. When patients are intolerant to ACEi due to angioedema attacks, angiotensin receptor blockers can safely replace ACEi.

List of original publications

- I. I. Rasmussen ER, von Buchwald C, Wadelius M, Prasad SC3, Kamaleswaran S, Ajeiy KK, et al. Assessment of 105 patients with angiotensin converting enzyme-inhibitor induced angioedema. *Int J Otolaryngol* 2017; 2017: 1476402.
- II. Rasmussen ER, Hallberg P, Baranova EV, Eriksson N, Karawajczyk M, Johansson C, et al. Genome-wide association study of angioedema induced by agents acting on the angiotensin system. Planned to be submitted July 2018.
- III. Cornwall JEL, Bygum A, Rasmussen ER. ACE-inhibitor related angioedema is not sufficiently reported to the Danish Adverse Drug Reactions Database. Planned to be submitted June 2018.
- IV. Rasmussen ER, Pottgård A, Bygum A, von Buchwald C, Homøe P, Hallas J. Angiotensin II receptor blockers are safe in patients with prior angioedema induced by angiotensin converting enzyme inhibitors – a nationwide registry-based cohort study. Planned to be submitted July 2018.