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PROTOCOL OPEN

Seinäjoki Adult Asthma Study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care

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BACKGROUND

Asthma is characterised by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory flow limitation.[1] Asthma can affect patients at any age with varying severities. Until recently, asthma has been considered to be a single, allergic, eosinophilic, T_H2-mediated and glucocorticoid-responsive disease.[2,3] Recently, cluster analyses have suggested that patients with asthma can be divided into different phenotypes, and the age at disease onset was found as a key differentiating factor between phenotypes.[2,3] Later- or adult-onset disease is less associated with allergy than asthma beginning in childhood. Adult-onset phenotypes such as late-onset eosinophilic (often severe), exercise-induced, obesity-related and neutrophilic asthma have been proposed.[2,3] Most publications on asthma have focused on allergic asthma starting in childhood.[2,3] The symptoms in childhood are often transient, and approximately three out of four asthmatic children will outgrow their asthma.[4] In contrast, the long-term prognosis of adult-onset asthma is not known, and only two[5,6] follow-up studies of duration of 2–5.8 years have been published and suggest a less favourable outcome. Thus, long-term, real-life, follow-up studies with asthma patients treated in primary care are needed. Allergic childhood asthma can usually be treated well by inhaled glucocorticoids,[2–4] whereas the need for different add-on therapies[7] is common in adult-onset disease and the therapeutic response may remain insufficient.[2,3,7] In adult patients with asthma, co-morbidities are common.[8,9] Still, a single-disease paradigm dominates randomised controlled trials, health policy, delivery and guidelines.[8] The current guidelines on diagnostics and treatment of asthma[1,10] or asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome[1,11,12] offer us advice and information mainly on the epidemiology, risk factors, diagnostic criteria, (initial) pharmacotherapy and treatment of exacerbations. However, when it comes to exact recommendations on whether the diagnostic studies and the diagnosis of asthma should be made in primary practice, the recommendations, if they exist at all, are based on opinion rather than on evidence. Furthermore, a similar lack of information remains when specific questions on the organisation of the follow-up of chronically ill patients with asthma are asked. Examples of such questions are as follows: who should perform the follow-up checks? How often should these follow-up checks be performed? Exactly what follow-up tools should be used?

AIMS

The aim of this study is to increase the understanding on the diagnostics and diagnostic process, organisation of the long-term asthma care, therapeutic outcomes, prognosis and the factors affecting the prognosis of new-onset asthma diagnosed at adult age.

METHODS

Study design, inclusion and exclusion criteria

Seinäjoki Adult Asthma Study (SAAS) is a single-centre (Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland) 12-year follow-up study of a total cohort of 259 patients having new-onset asthma that was diagnosed at adult age. However, two patients were excluded because they were later found to have a previous diagnosis of asthma during childhood, leaving 257 patients in the original cohort. The study was divided in two parts (Figure 1): the collection of the original cohort (phase I) and follow-up visit (phase II). The original cohort was collected between 6 October 1999 and 17 April 2002. Patients were referred to the hospital by primary-care practitioners because of suspicion of asthma. Inclusion and exclusion criteria are shown in Table 1. Patients with simultaneous asthma and COPD were not excluded, and the study population includes patients who could be defined as having asthma–COPD overlap syndrome, even though the inclusion criteria for those patients are not exactly the same as currently used criteria for asthma–COPD overlap syndrome.[1,11,12]

After 12 years, patients were invited to a follow-up visit (phase II; 10 December 2012 and 31 October 2013) in which asthma status, co-morbidities (chronic rhinitis or obstructed nose, allergic rhinitis or conjunctivitis, diabetes, hypertension, coronary heart disease, COPD and any other patient-reported disease), medication (including medication to other diseases and the disease treated), control, severity and lung function were evaluated (Figure 1). In addition to the data gathered at these visits, data on asthma follow-up visits, exacerbations, hospitalisations, possible occupationally induced asthma and prescribed asthma medication were collected from hospital clinics, primary health care, occupational health care and private practices for the whole 12-year follow-up period. In addition, the use of medication that was realised, i.e., medication bought from pharmacy, will be retrieved. In addition to asthma-specific factors, data include occupational, lifestyle and socioeconomic factors at the follow-up visit.

Ethical considerations and permissions

Phase I was originally designed as a registry serving as an asthma-related data exchange platform between primary and specialised care, as well as

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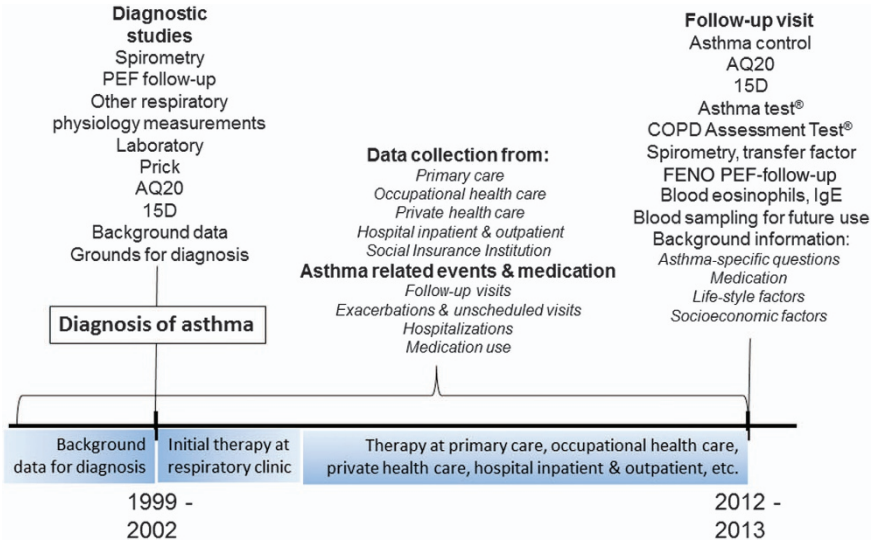

Figure 1. Schematic presentation of the Seinäjoki Adult Asthma Study. The original cohort (phase I) was collected between 6 October 1999 and 17 April 2002, and follow-up visit (phase II) was performed between 10 December 2012 and 31 October 2013.

Table 1. Inclusion and exclusion criteria used in SAAS

Inclusion criteria	● A diagnosis of new-onset asthma made by a respiratory specialist ● Diagnosis confirmed by at least one of the following objective lung function measurements:[a] ○ FEV_1 reversibility in spirometry of at least 15% and 200 ml ○ Diurnal variability (⩾20%) or repeated reversibility (⩾15%/60 l/min) in PEF follow-up ○ A significant decrease in FEV_1 (15%) or PEF (20%) in response to exercise or allergen ○ A significant reversibility in FEV_1 (at least 15% and 200 ml) or significant mean PEF change in response to a trial with oral or inhaled glucocorticoids ● Symptoms of asthma ● Age ⩾ 15 years
Exclusion criteria	● Physical or mental inability to provide signed informed consent ● Diagnosis of asthma below the age of 15 years ● Of note: ○ Patients with comorbidities, either other lung disease or any other significant disease, were not excluded ○ Patients were not excluded because of smoking, alcohol use or any other lifestyle factor ○ Respiratory symptoms or any other disease during childhood was not a reason to exclude patients, but a diagnosis of asthma at age < 15 years was an exclusion criteria

Abbreviations: FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; SAAS, Seinäjoki Adult Asthma Study.
[a]The objective lung function criteria reflect those of National and International Guidelines valid in 1999–2002 and may not exactly follow those valid at the moment.[1,10]

an asthma-related research registry. Phase I was part of hospital development projects (institutional permission TU 1114). No interventions outside normal clinical practice were carried out. All participants in the original cohort gave written informed consent to be included in the registry. With the development of a common regional electronic patient record system, the data exchange platform became unnecessary, but the research registry remained. The participants of the follow-up visit (phase II) gave written informed consent to the study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland (R12122).

Setting and background data

The organisation of asthma care in general and especially in the Seinäjoki Central Hospital district has recently been described in detail.[13] Asthma is a common disease needing community solutions.[14] The actions of the Finnish Asthma Programme[14,15] have been put into practice in the hospital district.[13,16] The original cohort (phase I) represents novel adult asthma cases well; for example, the total number of new diagnoses of asthma at the study centre in 2001 was 133.[16] Of those, 126 patients were recruited to phase I of this study, representing 94.7% of new diagnoses of asthma.

The main planned outcomes

Prognosis of new-onset asthma diagnosed at adult age during a 12-year follow-up. The questions the clinician is facing in front of an adult patient with newly diagnosed asthma are as follows: what is the prognosis of adult-onset asthma in general and especially in this particular patient? Are there any prognostic markers that would help me in predicting the future and guide me in planning his/her future therapy? The primary outcome is the prognosis of asthma (remission, control and severity). However, evaluation of control at a single time point does not represent the true morbidity of asthma.[17] Our intention is to characterise the true 12-year prognosis of asthma, i.e., cumulative burden of asthma-related events, which is the second primary outcome. Secondary outcomes include the following: exacerbations, hospitalisations and mortality because of asthma, multimorbidity, lung function and inflammatory cells (e.g., blood eosinophils and neutrophils), as well as inflammatory and other markers of interest[18–21] in the pathogenesis of asthma such as interleukins, adipokines and periostin (Figure 1).

Diagnostics and follow-up of patients with adult-onset asthma in primary and specialised care. The diagnosis of asthma with all patients

in the present study was confirmed by a respiratory specialist, but diagnostic studies for most patients were partly performed already in primary care. This gives us the opportunity to assess the proportion of diagnoses that could have been done already in primary care and the diagnostic tools that were able to provide sufficient information on the diagnosis of adult-onset asthma in primary care. All asthma-related follow-up visits over a 12-year period both in primary and specialised care are collected and evaluated. Thus, the impact of asthma follow-up visits on the outcome of asthma during a 12-year period can be assessed. This gives us a possibility to evaluate whether, e.g., the place or the performer, the timing or frequency of control visits and actions performed at the control visit can contribute to the outcome of asthma and how the care of chronic asthma should be organised.

Statistical analysis

Statistical analysis involves the basic statistical tools for continuous, categorical or dichotomous variables such as *t*-test, nonparametric tests (e.g., Mann–Whitney) and analysis of variance. To evaluate the associations between variables, χ^2-test, correlation matrixes and regression analysis will be used.[22,23]

Usually, the risk of asthma attacks is expressed as the total number of events per patient or as yearly incidence of events.[17] However, this analysis does not take into account the timing of asthma attacks in relation to changes in the other factors in asthma care (e.g., change in medication). Even though Cox regression analysis can also involve time-dependent variables, it will be inevitable to develop new ways to express the risk of asthma attacks in relation to other changes in the condition of the patient. Therefore, more sophisticated statistical methods will be included to illustrate these connections. Cluster analyses of patients with asthma have suggested that patients with asthma can be divided into different phenotypes.[24–26] However, the studies published thus far have been cross-sectional and analysed their subjects at one single time point or after only a short follow-up. Analysis of patient data with a long-term follow-up time with time-dependent incidents will require a more sophisticated way of performing cluster-type analysis. Thus, we will evaluate whether the long-term follow-up will identify new and/or different clusters among patients with adult-onset disease.

DISCUSSION

The characterisation of phenotypes of asthma is still in process.[2,3] As the phenotypes have been characterised relatively recently (i.e., between 2008 and 2014),[24–26] there has not been enough time for long-term follow-up studies to be conducted. Our recent published systematic literature review[27] identified only one follow-up study[5] of newly diagnosed adult-onset asthma lasting $\geqslant 5$ years. Another 2-year follow-up study of adult-onset asthma has been recently published.[6] Thus, the present study will increase our knowledge on the long-term prognosis of new-onset asthma diagnosed at adult age. The exclusion criteria in most studies with asthma are current smoking or smoking history $\geqslant 10$ pack-years, as well as the presence of co-morbidities. However, the therapeutic response in patients with asthma who smoke remains insufficient.[28,29] A recent survey[9] indicated that over 60% of asthma sufferers have one or more additional co-morbidities. Furthermore, these co-morbidities associate with unscheduled asthma care among adults.[8,9] The patient population generally included in clinical trials in asthma[7] has been shown to represent only 1.3–5.4% of those obstructive seen by a generalist.[30] In the present study, patients were not excluded because of smoking or any significant co-morbidity, suggesting that the study population more closely represents that seen by a generalist.

Asthma is a common disease needing community solutions.[14] Early diagnosis, active treatment and self-management are not possible without the active role of primary-care professionals. The key for the implementation of the Finnish Asthma Programme[14,15] was the primary-care network of local asthma co-ordinators (physicians and nurses) in local health-care centres.[13] The Finnish Asthma Programme reduced, e.g., the number of asthma hospital days and morbidity.[15,31] The published reports[15,31] give indirect evidence to support the primary-care-centred organisation of care of chronic asthma, but more evidence is needed. The Finnish Asthma Programme was extensively used in the Seinäjoki Hospital district and has been evaluated.[13,16,32–34] This allows us to evaluate the diagnostic process, as well as the follow-up visits made both in primary and specialised health care. According to the principles of the Finnish Asthma Programme,[13–15] a hypothesis to be tested is that the diagnostic evaluations in patients with adult-onset asthma can be performed in primary care. Similarly, another hypothesis, supported also by the literature,[35] is that specialised nurse-centred follow-up visits are important in the follow-up of most patients with adult-onset asthma.

DISCLAIMER

None of the sponsors had any involvement in the planning, execution, drafting or write-up of this protocol.

CONTRIBUTIONS

HK drafted the paper with contribution and approval from all authors. All authors have been actively involved in the study in different capacities. LET and HK planned and drafted the original study protocol with the help of TK in specific aspects concerning questionnaires, statistical planning and health economic matters. PI is responsible for data collection, storage and managing, and most of the data analysing processes, as well as drafting reports of the study.

COMPETING INTERESTS

HK reports personal fees and non-financial support from Almirall, personal fees from AstraZeneca, personal fees from Chiesi Pharma AB, personal fees from GlaxoSmithKline, personal fees and non-financial support from Boehringer-Ingelmheim, personal fees from Leiras-Takeda, personal fees from MSD (Merck Sharp & Dohme Corp.), personal fees from Novartis, personal fees from Mundipharma, personal fees from Medith, personal fees from Resmed Finland and non-financial support from Intermune, outside the submitted work. LET reports personal fees and non-financial support from Leiras-Takeda, personal fees and non-financial support from Mundipharma, personal fees and non-financial support from Novartis, and non-financial support from Boehringer-Ingelheim, outside the submitted work. The other authors declare no conflicts of interest.

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