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Health care situation in patients with allergic respiratory diseases with special focus on specific immunotherapy

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Summary
Background Allergic respiratory diseases have an impact on the performance and quality of life of the patients. The allergen immunotherapy (AIT) is the only causal treatment approach with the chance to positively influence the course of the disease. However, differentiated figures for the treatment of suitable patients in Germany are still missing.
Methods The health care situation in Germany is examined with a retrospective, cross-sectional, cohort-based health care analysis based on patient data and routine data from statutory health insurance (SHI). Characteristics are identified that encourage or prevent guideline-based care. In addition, data on quality of life and costs of illness of allergic rhinitis and allergic asthma are collected and evaluated.
Results Routine data provide comprehensive and cross-sectoral information about diagnoses and utilization of health care services. In addition, primary data give information on disease severity, treatment history, quality of life, use of alternative treatment methods, and sociodemographic characteristics of the patients.
Conclusion Analysis of the care situation with regard to the specific immunotherapy in cases of allergic respiratory diseases (VerSITA) provides a solid basis for future research and for informing decision-makers in order to develop measures to optimize care.

Keywords AIT · Allergen immunotherapy · Health services research · Asthma · Rhinitis

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Abbreviations

AA	Allergic Bronchial Asthma (study group)
ACT	Asthma control test
AIT	Allergen immunotherapy
AR	Allergic Rhinitis (study group)
AR & AA	Allergic Rhinitis and Allergic Bronchial Asthma (study group)
ATC	Anatomical therapeutic chemical
DLR	German Aerospace Center
DRKS	German Register of Clinical Studies
EQ-5D	EuroQol-5-Dimensions
ICD	International Classification of Diseases
OTC	Over-the-counter
PCN	Pharmacy central number
RTSS	Rhinitis Total Symptom Score
SCIT	Subcutaneous immunotherapy
SHI	Statutory health insurance
SIT	Specific immunotherapy

SLIT Sublingual immunotherapy
VerSITA Analysis of the care situation with regard to the specific immunotherapy in cases of allergic respiratory diseases

Background

Allergic respiratory diseases affect people of all ages and social classes and lead to restrictions in social life and schooling and work performance. As they frequently develop in childhood and adolescence and persist in most cases for years, often decades, optimal care is important from a social and economic perspective [1].

The therapy of allergic respiratory diseases includes, on the one hand, allergen avoidance, which often cannot be fully implemented and/or does not lead to efficient symptom control and, on the other hand, the drug treatment of symptoms. The only causal therapy approach with the ability to influence the natural course of the disease is specific immunotherapy (SIT) (also called allergen immunotherapy [AIT]). In addition to a lasting reduction of the symptom burden, drug use, and possibly the loss of productivity, AIT can also prevent the development of bronchial asthma in rhinitis patients and new sensitizations [2–5].

As part of AIT, patients receive allergens for a period of 3–5 years in the form of subcutaneous injections (subcutaneous immunotherapy [SCIT]) or sublingual application (sublingual immunotherapy [SLIT]). Since AIT has to be administered regularly over this period of time—approximate every 4–6 weeks in the case of SCIT and daily in the case of SLIT—and since the costs incurred are not offset by any treatment effects in the event of premature discontinuation of therapy, compliance is of central importance for achieving therapeutic effects and thus for cost-effective care [4]. In principle, AIT is indicated in patients over 5 years of age with a reliable allergy diagnosis and inadequate symptom control despite allergen avoidance, provided there are no contraindications. A prerequisite is that standardized allergens of high quality, whose effectiveness has been proven for the given indication and age group, are available. In addition, factors that increase the efficacy of AIT must be taken into account when determining the indication. These include short duration of the disease, low involvement of the lower respiratory tract, young age, and good compliance and adherence [4].

The treatment rates for AIT that have been reported so far for Germany are considered rather low [6, 7]. However, an exact comparison is made difficult because no studies on the number of patients with an indication for AIT are available for Germany. Optimal care of patients with allergic respiratory diseases, however, includes the usage of an AIT in all patients with a corresponding indication.

Methods

Design

The aim of the ongoing study "Analysis of the care situation with regard to the specific immunotherapy in cases of allergic respiratory diseases" (VerSITA) is an analysis of the care situation of patients with allergic rhinitis and/or allergic asthma with focus on AIT. The primary working hypothesis is the assumption of over- and undersupply of patients with allergic respiratory diseases with regard to the existence of an indication for AIT. The secondary working hypothesis is that over- and undersupply occurs more frequently in certain patient groups and that there are characteristics that significantly encourage or prevent (indication-appropriate) AIT. Furthermore, the deficient supply of AIT should be quantified and the severity of symptoms, quality of life and cost of illness in allergic rhinitis and allergic asthma should be reported descriptively. In order to present the care situation of AIT in patients with allergic rhinitis and allergic asthma, a retrospective, cross-sectional, cohort-based care analysis is carried out based on a postal patient survey and routine data from DAK-Gesundheit—a large, nationwide statutory health insurance (SHI) provider in Germany.

Analyses are based on a combination of patient survey data and the evaluation of SHI routine data. While the routine data provide comprehensive and cross-sectoral information on diagnoses and resource use, the patient questionnaires are used to collect data on the current care situation, the utilization of over-the-counter (OTC) drugs, and clinical characteristics that are used to assess the indication. In addition, data on the health-related quality of life, subjective control over one's own health, demographic patient characteristics and smoker status are collected through patient survey. Integrated in the VerSITA study questionnaire are the Asthma Control Test (ACT), the Rhinitis Total Symptom Score (RTSS) and the EuroQol-5-Dimensions (EQ-5D)—depending on the age of the study participant questioned in the EQ-5D-5L, EQ-5D-Youth and EQ-5D-Proxy versions. In the ACT, both the influence of asthma on the daily life of the patient and the type of (drug) control of asthma are retrospectively assessed for 4 weeks. The RTSS provides information on the severity of rhinitis by evaluating various symptoms of the disease. The EQ-5D is an internationally established generic index instrument to measure health-related quality of life.

The VerSITA study has been prospectively registered in in the German Register of Clinical Trials (DRKS-ID of the study: DRKS00017316). The items from the DRKS data set for the VerSITA study are given in Table 1.

Table 1 Items from the DRKS data set for the VerSITA study registration

1	DRKS-ID of the study: DRKS00017316
2	Date of registration in DRKS: 21 May 2019
3	Investigator Sponsored/Initiated Trial: yes
4	Ethics Approval: Approved
5	(Leading) Ethics Committee Template No.: 19-8598-BO, Ethics Committee of the Medical Faculty of the University of Duisburg-Essen
6	Investigated disease/health problem (ICD-10): J30.1, J30.2, J30.3, J30.4, J45.0, J45.8
7	Study type: Non-interventional, observational study
8	Study Design Allocation: Other
9	Blinding: Open
10	Primary endpoint: by questionnaire and routine data: presence of a deficient care situation with regard to AIT
11	Secondary endpoint: by questionnaire and routine data: patient characteristics correlating with a deficient care situation regarding AIT; health-related quality of life; cost of illness
12	Countries in which study participants are recruited: Germany
13	Included genders: all
14	Minimum age of inclusion: 5 years
15	Maximum age of inclusion: no maximum age
16	Further inclusion criteria for the group of insured persons with allergic rhinitis are: at least one confirmed outpatient diagnosis (J30.1, J30.2, J30.3 or J30.4) in at least one quarter; for the entire index period (01.07.2017–30.06.2018) as well as in the 4 previous years insured by DAK-Gesundheit
17	Further inclusion criteria for the group of insured persons with allergic asthma are secured outpatient diagnoses in two quarters and/or inpatient diagnoses in one quarter; prescribed at least one of the drugs listed below; insured by DAK-Gesundheit for the entire index period as well as in the 4 previous years. ATC codes Medication Asthma: R03AA, R03AC, R03AK, R03BA, R03BB, R03BC, R03CB, R03CC, R03DA, R03DC, R03DH, R03DX
18	Exclusion criteria: none
19	Primary sponsor: Institute for Healthcare Management and Reseach, University of Duisburg-Essen
20	Cooperation partners: DAK-Gesundheit; Deutsche AllergieLiga e. V.
21	Source of monetary support: Innovation Fund of the Joint Federal Committee (represented by: DLR)

AIT allergen immunotherapy, *ATC* Anatomical Therapeutic Chemical, *DLR* German Aerospace Center, *DRKS* German Register of Clinical Studies, *ICD* International Classification of Diseases

Table 2 Prescription drugs for diagnosis validation in bronchial asthma

ATC code	Description
R03AA	α- and β-adrenoceptor agonists
R03AC	Selective 2-adrenoceptor agonists
R03AK	Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics
R03BA	Glucocorticoids
R03BB	Anticholinergics
R03BC	Antiallergic agents, excluding corticosteroids
R03CB	Nonselective β-adrenoreceptor agonists
R03CC	Selective β2-adrenoreceptor agonists
R03DA	Xanthines
R03DC	Leukotriene receptor antagonists
R03DH	Homeopathic and anthroposophic remedies for systemic use in obstructive respiratory diseases
R03DX	Other systemic drugs for obstructive airway diseases

ATC Anatomical Therapeutic Chemical

Inclusion criteria

Based on inclusion criteria, a sample of insured persons with relevant diagnoses of allergic respiratory diseases (allergic rhinitis and/or allergic asthma) is drawn from the DAK-Gesundheit insured population in the period 01 July 2017 to 30 June 2018 (index period).

Inclusion criteria for the study population of individuals with rhinitis is a confirmed outpatient diagnosis of J30.1, J30.2, J30.3 or J30.4 in at least one quarter during the 12-month index period, as the majority of medical care for individuals with allergic rhinitis is provided on an outpatient basis. Diagnostic validation via drug use is not performed for this group as the treatment of symptoms is predominantly OTC medication, the costs of which have to be covered by the insured themselves and are not included in the routine data. Thus, the drug use documented in the routine data does not represent a suitable selection criterion for the insured with rhinitis (J30.1, J30.2, J30.3 or J30.4). Inclusion criterion for the study population of patients with allergic bronchial asthma are International Classification of Diseases (ICD) codes J.45.0 and J.45.8 in at least two quarters as a confirmed outpatient diagnosis and/or in at least one quarter as a confirmed inpatient diagnosis. In addition, the diagnosis is validated by the indication-specific drug prescriptions listed in Table 2, i.e. in addition to the presence of the outpatient diagnosis in at least two quarters or the presence of an inpatient diagnosis, at least one of the drugs listed in Table 2 must have been prescribed. Almost all drugs are prescription-only and are reimbursed by the SHI system, so that they are reflected in the drug prescriptions documented by the health insurance companies.

In addition to the (validated) ICD-10 diagnoses, the following inclusion criteria apply:

- at least 5 years old in the index period (01 July 2017–30 June 2018),
- over the entire index period as well as in the 4 previous years insured by DAK-Gesundheit.

There are no further exclusion criteria.

Groups/Study arms

In order to be able to comprehensively investigate the care situation with regard to AIT in Germany, it is necessary to already make group assignments during sampling on the basis of the routine data. When

Table 3 Relative and absolute sample size

	Rhinitis		Asthma		Rhinitis and asthma		Total	
	AIT	No AIT	AIT	No AIT	AIT	No AIT	AIT	No AIT
Sample size	12%	1.2%	100%	8%	60%	10%	–	–
Insured in the routine data	33,386	377,647	1123	48,403	6868	42,436	41,377	468,486
Insured in the patient survey	4006	4532	1123	3872	4121	4244	9250	12,648
Expected response rate of the patient survey	1202	1360	337	1162	1236	1273	2775	3794

AIT allergen immunotherapy

forming the groups, both the disease of the study participants and their AIT status are considered.

The identification of patients receiving AIT is based on the Anatomical Therapeutic Chemical (ATC) codes.

Since AIT is conducted over a period of at least 3 years, a review of drug prescriptions take place during the 4 years preceding the index period. Only patients in whom no AIT has been documented either in the index period or in the 4 years preceding it are assigned to the group without AIT treatment. To check plausibility, the patient questionnaire contains the question whether an AIT has already been performed and if so, in which period. On the basis of the above criteria, DAK-Gesundheit compiles a total of six pseudonym lists, divided into the groups "Allergic Rhinitis (AR) with/without AIT", "Allergic Rhinitis and Allergic Bronchial Asthma (AR & AA) with/without AIT" and "Allergic Bronchial Asthma (AA) with/without AIT". Random samples are drawn from the following six groups: 1. "AR with AIT in the index period and/or within the last 4 years prior to that", 2. "AR & AA with AIT in the index period and/or within the last 4 years prior to that", 3. "AA with AIT in the index period and/or within the last 4 years prior to that", 4. "AR without AIT in the index period and/or within the last 4 years prior thereto", 5. "AR & AA without AIT in the index period and/or within the last 4 years prior thereto", 6. "AA without AIT during the index period and/or within the 4 preceding years".

The form of application (SCIT or SLIT) as well as the dosage scheme are identified by the information on the pharmaceutical central numbers (PCN) (e.g., dosage form). In addition, the form of administration is recorded via the patient questionnaire. Random samples are taken from the previously mentioned selected groups. Each group must have a sufficient number of cases for statistical analysis. Therefore, the size of the random samples does not correspond to the actual distribution in the total population of the insured. In addition, different indication criteria apply to the three disease groups, e.g., partially or uncontrolled bronchial asthma is a contraindication. A differentiated consideration of the disease groups is therefore necessary. Table 3 gives an overview of the six groups mentioned above in terms of the absolute and relative number of insured persons. For example, every insured person from the group "AA with AIT" has to be contacted, since otherwise, due to the rare combination of characteristics, a sufficiently large sample would not be expected. From the group "AR without AIT" only 1.2% of the insured persons have to be invited to participate in the study. Regardless of the group affiliation, a response rate of 30% is assumed, based on conservative estimates. A total of 21,898 insured persons are asked to participate in the VerSITA study.

Patient recruitment

The selected insured persons are contacted and invited to participate in the study postal; at the same time, they receive a standardized questionnaire. A postal reminder is sent out later. All insured persons who have sent back a valid declaration of consent and an evaluable questionnaire are included in the analysis. With the postal consent to participate in the study, the insured persons also agree to the transmission of their routine data and give their written informed consent.

Procedure of data collection

The care analysis based on this sample also takes into account information on outpatient and inpatient treatment from the routine data of DAK-Gesundheit. In the analysis, the study participants are divided into four groups: "AIT with indication" (group a), "AIT without indication" (group b), "no AIT with indication for AIT" (group c), and "no AIT and no indication for AIT" (group d). An oversupply is expected in group b and an undersupply in group c.

A graphic summary of the above-mentioned derivation of the data basis for analysis from the survey and routine data is provided in Fig. 1. The responses from the survey are checked in a trust center with reference to a valid declaration of consent and pseudonymized.

In May 2019, a pretest is carried out in which the first insured persons are contacted so that the main survey is conducted from mid-June 2019.

Statistical analyses

After the survey and the routine data transfer, the following descriptive and deductive statistical analyses are performed at the Institute for Healthcare Management and Research at the University of Duisburg-Es-

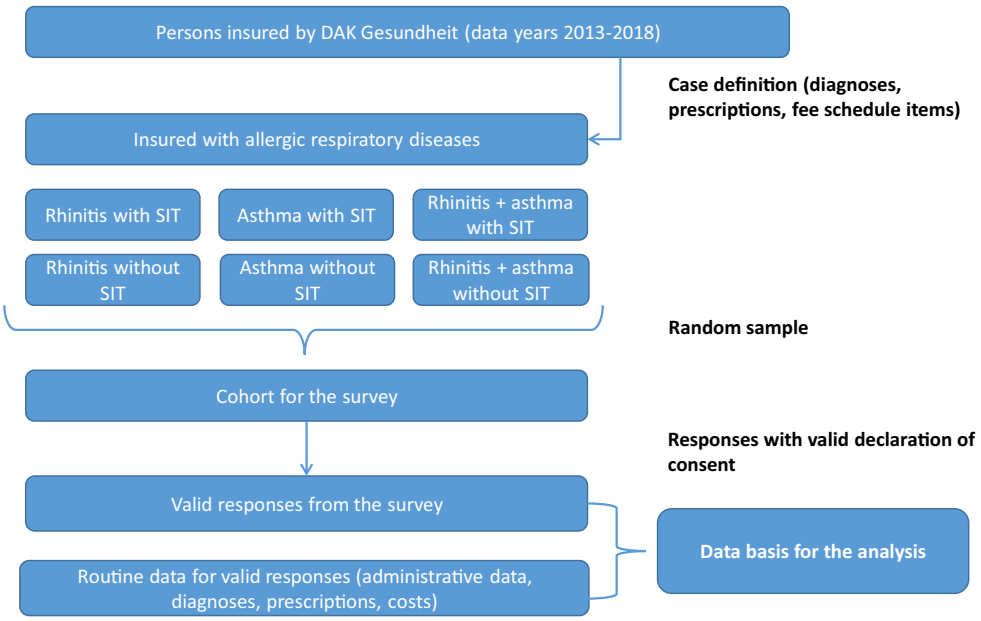

Fig. 1 Derivation of the data basis for the analysis. *SIT* specific immunotherapy

sen: Determination of significant differences between patient groups, quantification of oversupply and undersupply and thus optimization potential based on group classification, descriptive presentation of symptom severity, quality of life, and cost of illness in allergic respiratory diseases in general and in the above mentioned groups as well as identification of relevant predictive factors for an AIT using logistic regression analysis. Different significance tests are used depending on the type of variable and the form of distribution: Binomial test, t-test, Mann–Whitney U test, Kruskal–Wallis test and χ^2 test. To estimate the transferability of the results, the group of actual study participants is compared with the total collective of DAK-insured persons with allergic rhinitis and/or allergic asthma in the period July 1, 2017 to June 30, 2018.

Ethics

The routine data of the DAK-Gesundheit are made available to the Institute for Healthcare Management and Research exclusively in pseudonymized form. The inclusion of a trust center ensures that the Institute for Healthcare Management and Research only receives the data of the patient questionnaires in pseudonymized form, so that it is not possible to identify individual persons. Each questionnaire is accompanied by a declaration of consent for participation, which has to be signed by the patient or the legal guardian, and a patient information sheet explaining the aims of the examination as well as the use and processing of the patient-related data. With his/her signature, the patient or legal guardian agrees to the use of the data. Only questionnaires with a signed consent form are included in the analysis.

The survey is conducted in accordance with the principles written in the Declaration of Helsinki. The study design, patient information, consent form and questionnaire were submitted to the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen before the start of the survey (template no. 19-8598-BO). The ethics committee has given a positive ethics opinion.

The VerSITA study is financed exclusively by the Innovation Fund, which is represented by the German Aerospace Center (DLR) (funding code: 01VSF17042). No commercial interests are pursued by the VerSITA study.

The VerSITA study is registered in the DRKS (DRKS-ID: DRKS00017316).

Results

While the routine data provide comprehensive and cross-sectoral information on diagnoses and utilization of health services, the primary data from the patient questionnaires provide information on the current care situation and use of nonprescription drugs, the severity of the disease, therapy history, and quality of life as well as sociodemographic characteristics. On this basis, it is possible to identify predictive factors for oversupply and undersupply in which the groups differ significantly. On the one hand, the aim is to identify predictive factors for indication-appropriate care and, on the other hand, predictive factors for the implementation of an AIT. In this way, the deductive analyses can identify characteristics that encourage deficient care. On this basis, appropriate solutions can be developed. These solution approaches are to be processed in the form of recommendations for action.

Discussion

Previous studies on the AIT care situation focus on SCIT and are based on older data [6–8]. The proportion of patients indicated for AIT has been estimated in only one study so far [9]. For this estimate, the frequencies of guideline-based indication criteria were determined based on literature and supplemented by expert interviews. So far, no studies have been conducted to determine whether the therapy was indicated in the patients treated. The VerSITA study will close this gap. Therefore, this research project can for the first time offer a comprehensive and up-to-date care analysis and, by including clinical patient characteristics, provide information about indication-related deficient supply.

Furthermore, for the German population with allergic respiratory diseases, there is no comprehensive information available on disease costs, symptom severity and preference-based quality of life.

Risk factors of this patient survey are a low response rate and a correspondingly low number of cases. This risk should be minimized by assuming a rather conservative response rate in case number planning, a generous time window for answering and a reminder concept. With the reminder concept, patients are given the opportunity to receive all documents again so that a possible loss of documents does not lead to nonresponse.

In general, the estimation of the case numbers of the four analysis groups for the identification of deficient care is faced with the difficulty that the frequencies of oversupply and undersupply are not known yet. The present study is the first to collect data on this issue. This fact is taken into account in the planning of the number of cases in order to achieve a high number of cases and to be able to guarantee subgroup analyses.

Furthermore, the patient questionnaire used represents a combination of validated instruments and study specific questions, so it is not validated as a whole. Therefore, the entire questionnaire is subjected to a pretest procedure. Since the survey is conducted independent of the seasons, the assessment of symptom severity and quality of life cannot be carried out for all patients on a symptomatic day. In addition, these characteristics should refer to the period before the onset of AIT in patients with AIT. Therefore, the formulation of the questions is adapted in such a way that they are to be answered in relation to a period with clear allergy symptoms and, if necessary, before the onset of AIT. If caregivers fill out the questionnaire for children, there is a risk of distorting the answers, so that the actual severity of symptoms or the actual quality of life of the patient is not reflected. This risk is counteracted by using appropriate validated versions of the EQ-5D. Although the instruments for measuring symptom burden are not available in an adapted pediatric version, they are used in observational and clinical studies also in children and are recommended for conducting such studies.

Moreover, by combining the different data (survey and routine data), weaknesses of individual data sources can be compensated and additional information can be used to make statements with higher validity than would be the case if only one of these data sources were used.

VerSITA provides a solid basis for future research and for informing decision-makers in order to develop practical and effective measures for optimizing AIT care in allergic rhinitis and allergic asthma.

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