ALERGODATA: Sentinel registry of health outcomes in allergic patients treated with biological therapies from specialized allergology clinics in Spain.

INTRODUCTION

The incidence of allergic diseases has grown steadily in recent decades, generating a global public health problem that significantly impacts health and available healthcare resources [1]. If current epidemiological trends continue, the European Academy of Allergology and Clinical Immunology (EAACI) predicts that in less than 15 years, more than half of the European population will develop some type of allergy[2]. This increase in prevalence may be due to multiple factors, including advances in diagnostic techniques, new allergens, greater population, environmental pollution, changes in dietary habits, and the hygiene hypothesis. These diseases are caused by an exaggerated and inappropriate immune response to substances that are harmless to most people. They are clinically expressed as chronic processes that affect patients' quality of life, both physically and psychologically, influence their choice of professional or leisure activities, and require visits to an allergist specifically trained to diagnose and treat these diseases. The significant health and socioeconomic consequences of allergic diseases have galvanized many social groups, public awareness has increased, the political class is taking notice, and patient associations are being formed [3].

Thanks to a greater understanding of the complex immunological mechanisms underlying the etiopathogenesis of these diseases, numerous therapeutic options have emerged that have helped improve the quality of life of allergic patients, especially those with the most debilitating and poorly controlled manifestations [4, 5]. These treatments include biological drugs that select specific immune system targets. The biological agents currently approved in allergic diseases target IgE and cytokines or their receptors, such as IL-4, IL-5, and IL-13 [6, 7], but other potential biologics in this area are expected to appear on the market shortly.

Marketing a drug for use as a therapeutic agent requires clinical trials. Although these trials are crucial for approval, their limitations are well known [7, 8]. Biases are inherent in how their therapeutic effect has to be unequivocally demonstrated in patients selected explicitly for this purpose. These cohorts rarely represent the most complex phenotypes in routine clinical practice, and the experimental setting seldom reflects the less controlled conditions in which specialized care is conducted.

Once the drugs have been approved for marketing, observational studies must be conducted in routine clinical practice. One of the objectives of studies of this type is to analyze the risk-benefit ratio of such intervention in the real-world population. These studies require less time and less investment and collect information from heterogeneous population groups beyond the rigorous conditions of a clinical trial [8, 9]. Real-life surveillance of the behavior of a drug in a patient avoids the Hawthorne effect, i.e., when improvement is experienced simply as a response to being observed.

The European Medicine Agency (EMA) defines registries as organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure that is followed over time. [10]. These studies collect large amounts of

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data on the beneficial or detrimental effects of a given treatment on many patients in a short time [11].

In this context, the Spanish Society of Allergology and Clinical Immunology (SEAIC) has transformed its strategic vision into an action plan to provide evidence-based data on health outcomes in managing major allergic diseases in routine clinical practice. One of these activities is the Alergodata Registry, the first registry designed to obtain data on the use of biological drugs in severe asthma and/or chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis (AD) in patients attending specialized allergology clinics throughout Spain.

Alergodata registry: obtaining key health outcomes in therapeutic decision-making

The COVID-19 pandemic highlighted the commitment of Spanish allergists to providing specialized care in an extreme situation that overwhelmed the response capacity of national health systems worldwide. Spanish allergists as a group came out of the COVID-19 crisis strengthened by their commitment to the care of hospitalized patients, and their scientific society became more aware of the importance of the ongoing assessment and maximization of the efficacy of resources would take on in the future.

The public administration, medical associations, and scientific societies must play an active role in evaluating health outcomes resulting from high-value therapeutic decisions and their implications for the future and well-being of patients. These decisions are being made in a real-world situation where resources are limited and far removed from the experimental conditions in which the drugs first demonstrated efficacy and safety. An essential approach to obtaining a balanced view of the study results, then, is to complement the experimental findings with a sentinel surveillance system that should be a joint initiative of both public administrations and scientific groups, conducted throughout the National Health System (NHS), from an ongoing multicenter and multidisciplinary approach. In this way, the “live” experience of health outcomes in a real-world setting will be collected and examined to optimize decisions on available resources, thus improving the quality of care.

Health outcome registries are essential for therapeutic decision-making. That is the aim of the Alergodata Registry, a SEAIC initiative implemented at the end of 2019 that includes both adult patients and over five years old children. The Alergodata registry aims to describe the use of biological treatments as a treatment for allergic disease globally. Specifically, the main objective of the study is to describe the profile of patients with severe asthma and/or chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis who are receiving biological drugs and are followed up in specialized allergology clinics.

Secondary objectives include the following:

1. To describe the profile of patients with severe asthma attending specialized allergology clinics who receive or do not receive biological treatment.
2. To evaluate the efficacy of biological drugs in treating patients with severe asthma and/or chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis who are followed up in specialized allergology clinics.

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3. To evaluate the safety of biological drugs treating patients with severe asthma and/or chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis who are followed up in specialized allergology clinics, according to their risk management plan.
4. To describe the use of drugs of other types to control patients with severe asthma and/or chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis who are followed up in specialized allergology clinics.

More specifically, the aim is to observe the phenotypic profiles that are associated with the expression of certain allergic diseases most frequently seen in specialized allergology clinics, regardless of whether they are treated with biologics; and to assess the specific benefits of the different therapeutic strategies. The cost of treatments with biological drugs for diseases as prevalent as those in the registry means that balanced, ongoing observations are needed to optimize the efficiency of therapeutic decisions. Given the chronic and complex nature of these diseases, follow-up must be ongoing, and experience in routine clinical practice helps confirm or, if necessary, complement data on the incidence of adverse events, safety profiles, and response in terms of effectiveness. Comparing the different therapeutic alternatives in health outcomes will help establish more consistent and efficient criteria for using these drugs, thus improving the sustainability and quality of the health system.

DESIGN AND METHODS

The objectives of the SEIAC Strategic Plan inspire the proposed Alergodata Registry design. The aim is to provide a cross-sectional tool to all Spanish NHS allergy departments to promote participation and knowledge-sharing among allergists and critical thinking surrounding the use of biologics as a therapeutic alternative in some of the major diseases of the specialty. The registry includes severe asthma, chronic rhinosinusitis with nasal polyps, chronic urticaria, and moderate-severe atopic dermatitis.

Analyzing health outcomes resulting from specialist therapeutic decisions in patients with broad phenotypic expressions usually treated in allergy departments is constantly at odds with the evidence gleaned from controlled studies conducted in particular, homogeneous populations. That raises critical questions on how and when to start treatment with an acceptable risk-benefit ratio while considering the limitations of the National Health System accessibility and equity, driven by cost-effectiveness criteria and other factors. The strategic foundations proposed by the Alergodata design are intended to:

1. Sensitize researchers toward regularly recording patient data to obtain a shared overview of how the best outcomes may be achieved. That makes the patient the focus of a therapeutic decision, which is taken at the specialist's discretion but shared with the patient based on reliable experiences based on routine clinical practice.
2. Inform the scientific community, patients, and the public administration of the benefits of an ongoing "live" registry as an indicator of the current situation and the future

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direction of allergists' therapeutic decisions beyond the controlled outcomes of clinical trials.

3. Analyze the diseases studied in the registry: since these pathologies present different clinical and prognostic realities, it seems pertinent to foster a critical discussion on the use of biological therapies through discussion forums that place the specific focus of each disease in the context of the indication of biological therapy, while safeguarding principles of equity, access, and sustainability.

Registry coordinator team

The Alergodata Registry is a SEAIC initiative led by a project coordinator team that implemented this initiative (see Table 1).

Table 1. Alergodata Registry coordinator team

Antonio Valero Santiago	Hospital Clínic de Barcelona
Darío Antolín Amérigo	Hospital Universitario Ramon y Cajal, Madrid
Carmen Vidal	Complejo Hospitalario Universitario de Santiago de Compostela, Coruña
Javier Montoro	Hospital de Llíria, Valencia

The project coordinator plays a crucial role in facilitating and running the registry designed to answer clinically relevant questions and/or propose new approaches of empirical research based on the outcomes, while the coordinators have committed to implementing the registry and validating any modification of it. They have taken joint responsibility for preparing interim and final reports and contributing to the design and dissemination of the study results to the specialized scientific community they represent. Alergodata is being conducted and coordinated by specific committees for each disease (see Table 2).

Table 2. Specific committees for each of the diseases that are included in the Alergodata Registry

Scientific Committee	
Severe asthma	Julio Delgado
	Javier Domínguez
	Silvia Sanchez-Garcia
Chronic rhinosinusitis with nasal polyps	Carlos Colás
	Alfonso del Cuvillo
Chronic urticaria	Ignacio Jáuregui
	Beatriz Veleiro
Moderate-severe dermatitis	Milagros Lázaro
	Anna Sala

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Definition of registry patients

Patients who give their consent may be included in the registry if they fulfill all the inclusion criteria and none of the exclusion criteria (see Table 3). In this respect, the definition of admissible diagnoses is explicitly stated as a criterion of inclusion in the study. These patients must be under consideration for treatment with biological drugs according to the indication approved in the Spanish Summary of Product Characteristics (SPC) at the time of study inclusion.

Table 3. Selection criteria for Alergodata Registry patients

Inclusion criteria
• Adult patients or children over six years with a diagnosis of severe asthma, whether or not treated with biological drugs according to the SPC approved in Spain*. • Patients diagnosed with chronic rhinosinusitis with nasal polyps and/or chronic urticaria and/or moderate to severe atopic dermatitis that receive treatment with biological drugs according to the SPC approved in Spain*ǂ. • Patients that are seen in allergology clinics. • Patients who have signed informed consent to participate in the study.
Exclusion criteria
• Patients with a medical or psychological disorder that could limit their ability to understand and/or answer questions and complete questionnaires or patients who, in the opinion of the investigator, are unlikely to collaborate sufficiently.

*All biological drugs approved in the SPC approved in Spain at the time of the inclusion of the patient to the study may be included in the registry.

ǂ The age of inclusion will be determined according to the SPC approved in Spain* for the different biological drugs in each disease.

Severe asthma

Severe asthma is asthma that has required high doses of inhaled corticosteroids and a second maintenance drug [long-acting beta-adrenergic agonist (LABA) or leukotriene receptor antagonist] during the previous year or systemic corticosteroids for at least 50% of the previous year to prevent the onset of poorly controlled asthma, or poorly controlled asthma despite this treatment. Adult and pediatric patients over six years of age diagnosed with severe asthma who require at least one treatment with a combination of high-dose ICS/LABA (GEMA 5.0 or GINA 4-5 steps 5-6) will be included. Asthma patients will be included regardless of whether or not they need biological treatment [12].

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Chronic rhinosinusitis with nasal polyps

It is defined as the presence of two or more of the following symptoms: nasal obstruction, nasal congestion, runny nose, facial pressure or pain, and loss of smell for more than 12 weeks, and evidence on endoscopy or tomography of nasal polyps.

Chronic spontaneous urticaria

It is defined as the daily or almost daily presence of wheals and/or angioedema for at least six weeks that remains poorly controlled despite continuous antihistamine treatment at doses up to 4 times higher than those approved in the SPC.

Moderate-severe atopic dermatitis

It is defined as AD with a score greater than 25 on the SCORAD index, an EASI score ≥16 and/or an IGA score ≥3, and body surface area (BSA) involvement of at least 10%, despite topical treatment of appropriate strength.

Another exclusion criterion for patients with diagnoses of diseases studied in the registry is any medical or psychological disorder that could limit their ability to understand and/or answer the questions and complete the questionnaires. Similarly, patients who, in the investigator's opinion, are unlikely to collaborate sufficiently with the registry's requirements will be excluded.

As Alergodata is a live registry, each of the definitions of the different diseases under study will be updated to the newest guidelines published.

STUDY PLANNING AND SCHEDULE

The impact of the COVID-19 pandemic on the Spanish NHS's healthcare conditions led to growing restrictions and concerns surrounding public health and drastically limited the number of in-person visits to doctors' offices. These visits were largely replaced by various forms of remote care, including phone or video calls. This situation was experienced to varying degrees in the different autonomous communities. In response, the Alergodata Registry investigators decided to adopt alternatives for managing clinical studies, as proposed in the June 29, 2020, update of the AEMPS instructions for conducting clinical trials in Spain, which included the possibility of remotely signing informed consent and administering questionnaires. This policy sets down the instructions for the procedure by which the principal investigator contacts the patient by telephone to inform them in detail about the study. Oral consent may be obtained (by telephone or video call, for example) and documented in the patient's medical record and subsequently ratified in writing by the signature of the patient and the investigator. The principal investigator, or their designee, should send the patient information sheet (PIS) and informed consent form (ICF) to the patient by email or courier.

The procedure detailed how the signature of the patient's and the investigator's signatures could subsequently be ratified in writing by mail, audiovisual methods, or digital images. The patient was also allowed to scan the signed ICF and send the document by email or take a photo and send it to a mobile phone accessible only to the research team so that the image could be printed and included in the investigator's file as proof of signature. This same process was adopted as an alternative to follow-up visits.

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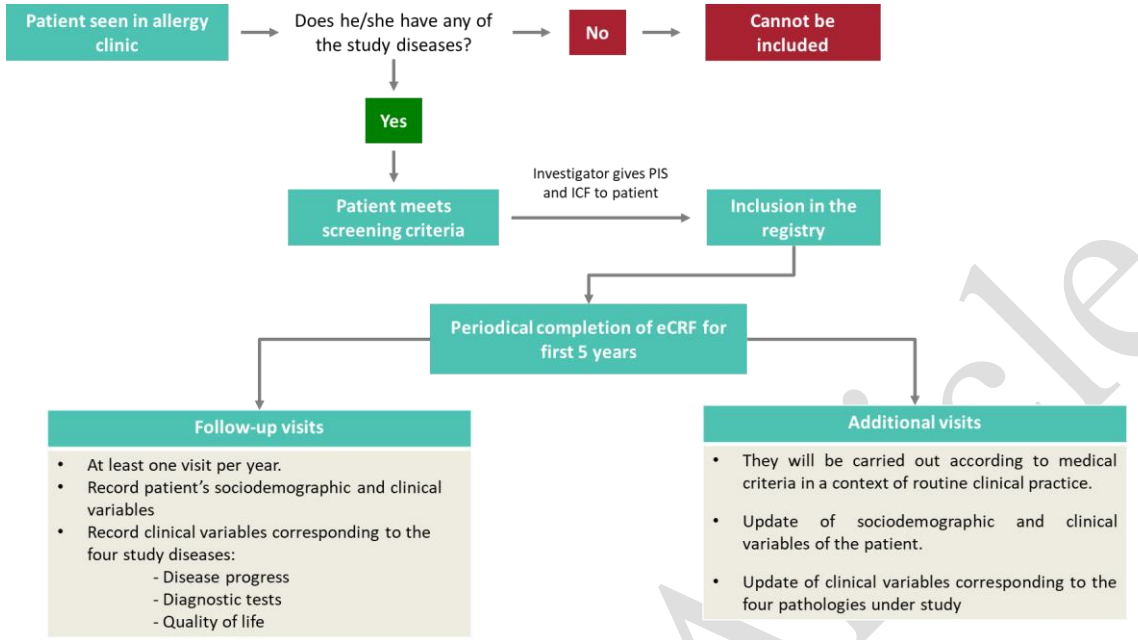

Figure 1. Study schedule

Patients treated in the allergy clinics of the hospital departments that agree to participate in this SEAIC-sponsored study must have a diagnosis, or their diagnosis must be confirmed before their inclusion in the registry. They must be informed of the option to participate in the study before the procedures required for their participation are evaluated. If they meet these requirements, the investigator provides the patient with the information sheet, focusing on the essential aspects for their understanding before their consent to participate is signed. Once the ICF has been signed, the inclusion criteria according to protocol requirements are recorded and the patient begins the study schedule and participation procedures. The schedule includes an inclusion visit and at least one annual visit for the first five years initially, as required by the disease. According to routine clinical practice, other visits will be conducted at the treating physician's discretion. The investigator records the information in an electronic case report form (eCRF) designed specifically for the study. Thus, the investigator completes quality of life and treatment satisfaction questionnaires according to the patient's responses. Similarly, investigators enter the results of questionnaires and tests in the eCRF (see Figure 1).

REGISTRY VARIABLES

The initial registry visit includes the collection of investigator identifiers, patient sociodemographic variables, and formal confirmation of compliance with all the inclusion criteria and none of the exclusion criteria, absence of any circumstances that might prevent the adequate follow-up of the registry, and patient sociodemographic profile and baseline clinical

situation. Baseline clinical laboratory variables, diagnostic tests, and the initial quality of life of the patient are also recorded.

As mentioned above, clinical and laboratory variables will be registered in successive annual visits, additional tests required as a result of improvements or worsening will be recorded, and the different quality-of-life questionnaires will be self-administered. The profile of each of the diseases requires specific clinical variables and follow-up questionnaires.

Effectiveness evaluation

Effectiveness will be measured according to the usual determinations made for monitoring and evaluating the patient in the follow-up of their disease. In the case of **severe asthma**, the GEMA 5.0 guidelines are used; the degree of asthma control (controlled, partially controlled, uncontrolled) will be classified according to Asthma Control Test (ACT); pulmonary function will be measured by forced spirometry + bronchodilation test; the number and intensity of exacerbations and use of systemic corticosteroids will be noted [13, 14]. In patients with **chronic rhinosinusitis with nasal polyps,** progress will be evaluated based on the improvement of nasal symptoms, including nasal congestion, discharge, facial symptoms, including the sensation of pressure and pain, and loss of olfactory capacity. Improvement in nasal symptoms will be assessed using a Likert-type subjective perception scale from 0 to 3 for duration and intensity or the Total Nasal Symptom Score (TNSS) [15], with four questions scored on a Likert scale of 0 (no symptoms) to 3 (severe symptoms) (minimum 0, maximum 12). Nasal obstruction and reduction in polyp size will be measured by endoscopy for the nasal passages and CT for the paranasal sinuses. In patients with **chronic urticaria**, the Urticaria Activity Score (UAS and UAS7) will be evaluated [16]. A score for the intensity of itching and number of wheals on a Likert scale of 0 to 3 (minimum score 0, maximum score 6) in a day will be calculated. UAS 7 refers to the sum of the daily UAS scores for seven consecutive days (minimum score 0, maximum score 42). The UCT scale (Urticaria Control Test) refers to the last four weeks: 4 questions (physical symptoms, quality of life, effectiveness of treatment, and disease control), assessed on a Likert scale from 0 (very severe involvement) to 4 (no involvement) for a score of 0-16 (0: no control, 16: full control) [17, 18]. In patients with **moderate to severe AD**, the Eczema Area Severity Index (EASI) and Scoring Atopic Dermatitis (SCORAD) will be calculated [19], and the intensity and extent of skin inflammation and the set of objective and subjective symptoms associated with the disease will be determined. The Investigator Global Assessment (IGA) and the Patient-Oriented Eczema Measure (POEM), scored on a scale from 0 to 4, will also be included in the evaluation [20] [21].

Safety evaluation

Safety will be assessed by recording adverse events according to the risk management plan of each biological drug.

Assessment of quality of life

In patients with **severe asthma**, quality of life will be measured using the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)[22], with 15 questions scored on a Likert scale of 1 (totally limited) to 7 (not limited) (minimum 15, maximum 105). For patients with **chronic rhinosinusitis with nasal polyps**, quality of life will be measured using the Sino-Nasal Outcome Test (SNOT22) [23, 24], with 22 questions scored on a Likert-type scale of 0 (no problem) to 5 (worst problem

possible) (minimum 0, maximum 110). In the case of patients with **chronic urticaria**, quality of life will be measured using the Chronic Urticaria Questionnaire for Quality of Life (CU-Q2oL)[25], with 23 questions scored on a Likert scale of 1 (none) to 5 (very much) (minimum 23, maximum 115), or the Dermatology Life Quality Index (DLQI)[26], with ten questions scored on a Likert scale of 0 (none) to 3 (very much) (minimum 0, maximum 30). Finally, for patients with **moderate to severe atopic dermatitis**, quality of life is assessed using the Dermatology Life Quality Index (DLQI) [26], with ten questions scored on a Likert scale of 0 (none) to 3 (a lot) (minimum 0, maximum 30), or the Children's Dermatology Life Quality Index (CLDQI)[27], with ten questions scored on a Likert scale of 0 (nothing) to 3 (very much) (minimum 0, maximum 30).

Quality and control of recorded data

As discussed, each investigator at the participating sites must include outpatients from their allergology practices who meet the inclusion criteria. At least one visit a year is required during the first five years, during which investigators will collect the information required by the eCRF.

The investigator will record the variables required to achieve the study objectives on the Web using an electronic CRF (eCRF) designed specifically for the study. The CRF can be downloaded from the Web and printed to make patient visits more agile and to avoid upsetting the investigator's routine clinical practice. Data can then be collected in paper format and subsequently recorded in the eCRF. All CRFs are identified by the investigator code, the patient code, and the date that the data is recorded. This data is automatically registered in the eCRF and becomes the internal entry into the system. It cannot be modified and marks the start of traceability and data security processes.

The data recorded in the study eCRF will be stored in a secure database and periodically reviewed by the study monitor to detect errors or missing data. This database will include ranges and internal consistency rules to check for correct data completion and quality. The study monitor will periodically list any missing variables that must be recovered by the investigator whenever possible. Any changes made to the database after the recovery of these data will be recorded.

STATISTICAL PLAN

An annual systematic statistical analysis of the Alergodata registry is planned to evaluate the primary and secondary objectives described in the protocol. This analysis will be stratified according to the disease(s) registered for each patient.

Study statistics will be presented in a global report, which will provide an overall analysis of the progress of the patients and their characteristics, and a specific report that will conclude the effectiveness and safety of the drugs. Data analysis will be performed using R language, version 3.3.2 or later, and a significance level of 0.05 will be used in all statistical tests performed on the outcome variables. Mean, standard deviation, median and interquartile range will be used to describe continuous variables, as appropriate. The number and percentage of patients by response category will be used to describe categorical variables.

The Alergodata protocol plans to analyze three population groups:

- **Population A** consists of all patients who meet the inclusion criteria with at least two evaluations per year (initial and at 12 months (+/-2) approximately) and are treated with

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biological drugs. Then the effectiveness of the biological drugs used and patient progress will be evaluated in this population group.

- **Population B** consists of all patients who meet the inclusion criteria but attend only one initial visit or one initial visit and follow-up less than or longer than the stipulated time (12 months (+/-2)) and are treated with biological drugs. In this population, the characterization of the patient profile at the inclusion visit will be evaluated.
- **Population C** consists of all patients with severe asthma who meet the inclusion criteria but attend only one initial visit or one initial visit and follow-up less than or longer than the stipulated time (12 ± 2 months). This population is used to characterize the profile of patients with severe asthma with or without biological treatment

The design has some limitations due to the nature of the data source and the analytical methodology applied, since the study data are collected from real clinical practice situations and recorded by the participating researchers. For this reason, the sample size will depend exclusively on the fluctuating numbers of patients attending visits. As a result, statistical tests and their power may be limited to the sample size collected during analysis. Before starting data analysis, a statistical analysis plan (SAP) will be made detailing all the analyses that will be performed, which the study sponsor must approve.

STUDY CONDUCT

All SEAIC member physicians were invited to participate. Sixty-two hospitals stated their interest in participating, representing the vast majority of Spanish National Health System allergology departments. Administrative procedures for implementing the patient registry were initiated, and 61 hospitals finally confirmed participation (see Table 4 at the end of the document).

During 2020, the COVID-19 pandemic coincided with the implementation of the research protocol, affecting to some degree the preparation of the project and requiring an atypical project launch that had to be adapted to the unusual scenario unfolding in hospital care. The research protocol was drafted, and the documentation was prepared and presented to the health authorities. At the end of the year, the Spanish Agency for Medicinal Products and Medical Devices (AEMPS) classified the registry as a post-authorization prospective follow-up study (EPA-SP).

During the first quarter of 2021, the protocol was evaluated by the autonomous community health agencies and Research Ethics Committees (RECs) of the hospitals that had confirmed their interest in participating in the SEAIC initiative, and the favorable opinion of the REC of the Hospital Clinic de Barcelona was obtained on March 4, 2021. The study was eventually filed or evaluated in 13 autonomous communities (see Table 5).

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Table 4. Hospitals participating in the Alergodata Registry

IdCentro	Hospital	Full name PI
1	Hospital Clínic de Barcelona	Antonio Valero
2	Hospital Universitari Vall d'Hebron, Barcelona	Anna Sala Cunill
3	Hospital Universitari de Bellvitge, Barcelona	Mº Teresa Dordal Culla
4	Hospital Universitario Germans Trias i Pujol, Barcelona	Albert Roger Reig
5	Hospital Sant Joan de Deu, Barcelona	Jaime Lozano Blasco
6	Consorci Sanitari de Terrassa, Barcelona	Marta Viñas Domingo
7	Hospital de Sant Joan de Déu de Manresa, Barcelona	Lidia Farrarons Lorente
8	Hospital Santa Maria de Lleida	Lluis Marqués Amat
9	Hospital Universitari Joan XXIII de Tarragona	Gaspar Dalmau Duch
10	Hospital Universitario Ramón y Cajal, Madrid	Carmen Vidal Albareda (IP)
11	Hospital Universitario La Paz, Madrid	Santiago Quirce Gancedo
12	Hospital infantil Universitario Niño Jesús, Madrid	Sílvia Sánchez García
13	Hospital Universitario del Sureste, Madrid	Rafael Pineda Pineda
14	Hospital de Torrejón de Ardoz, Madrid	Laura Vázquez Fuertes
15	Hospital Universitario Fundación Alcorcón, Madrid	Ana María Nieto Nieto
16	Hospital Central de la Cruz Roja San José y Santa Adela, Madrid	Jose Julio Laguna Martínez
17	Hospital Universitario La Princesa de Madrid	Mª Victoria Múgica García
18	CHUS-Complejo Hospitalario Universitario de Santiago, La Coruña	Virginia Rodríguez Vázquez
19	Complexo Hospitalario Universitario A Coruña	Antonio Parra Arrondo
20	Hospital Da Costa Burela (Hospital Da Mariña), Lugo	Nicola Giangrande
21	Hospital Provincial de Pontevedra	Tania Liñares Mata
22	Hospital Meixoeiro, Vigo, Pontevedra	Angela Meijide Calderón
23	Hospital de Llíria, Valencia	Javier Montoro Lacomba
24	Hospital Universitario de La Ribera, Valencia	Juan José Liñana Santafé
25	Consorci Hospital General Universitari de Valencia	Maria Dolores de las Marinas Alvarez
26	Hospital Universitario Dr. Peset, Valencia	Carmen Pérez Francés
27	Hospital Universitario de la Plana, Villarreal, Castellón	David El-Qutob López
28	Hospital Universitario del Vinalopó, Elche, Alicante	Mónica Antón Gironés
29	Hospital Universitario de Torrevieja, Alicante	María Dolores Martos Calahorro
30	Hospital Vega Baja, Orihuela, Alicante	Angel Ferrer Torres
32	Hospital HLA Jerez Puerta del Sur, Jerez de la Frontera, Cádiz	Antonio Letrán Camacho
33	Hospital Universitario Virgen Macarena, Seville	Pedro Guardia Martínez
34	Hospital Universitario Virgen del Rocío, Seville	Robledo Ávila Castellano
36	Hospital Materno Infantil HRU de Málaga	Candelaria Muñoz Román
37	Hospital Regional Universitario Carlos Haya/Hospital Regional Universitario de Málaga	José María Vega Chicote
38	Hospital Universitario de Jaén	Blanca Sáenz de San Pedro Morera
39	Hospital QuironSalud Córdoba	Ignacio García Núñez
40	Hospital Universitario Clínico San Cecilio, Granada	J. Fernando Florido López
41	Hospital HLA Inmaculada, Granada	Isabel Fernández de Alba Porcel
42	Hospital Clínico Universitario Lozano Blesa, Zaragoza	Juan Fraj Lázaro
43	Hospital Universitario Cruces, Vizcaya	Ignacio Jáuregui
44	Hospital Universitario Donostia, Guipúzcoa	Susana Lizarza Mendizábal
45	Hospital Universitario de Araba, Álava	Eduardo Fernández Ibañez
46	Complejo Asistencial de Zamora	José Camilo Martínez Alonso
47	Hospital Universitario de Burgos	Pedro Carretero Anibarro
49	Hospital El Bierzo, León	Beatríz Fernández Parra
50	Hospital General Rio Carrión, Palencia	Susana Cabrerizo Ballesteros
51	Hospital Universitario de Salamanca	Ignacio Dávila
52	Hospital Virgen del Valle, Toledo	Isabel María Sánchez Matas
53	Hospital Nuestra Señora del Prado de Talavera de la Reina, Toledo	Álvaro Moreno Ancillo
54	Hospital General Universitario Ciudad Real	Pedro Galindo Bonilla
55	Hospital General de Villarrobledo, Albacete	Ana Montoro Ferrer
56	Complejo Hospitalario Universitario Albacete	Patricia Prieto Montaño
58	Hospital Ciudad de Coria, Cáceres	Beatriz Hierro Santurino
59	Complejo Hospitalario de Mérida, Badajoz	Alicia Habernau Mena
60	Hospital Universitario de Badajoz	M. Ángeles Gonzalo Garijo
62	Complejo Universitario Insular Materno infantil de Gran Canaria, Las Palmas	Dara Martínez Beltran
63	Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife	Ruperto González Pérez
64	Hospital General Universitario Morales Meseguer, Murcia	Ana Mora Gonzalez
65	Hospital Universitario Rafael Méndez, Murcia	Sheila Cabrejos Perotti
66	Hospital Público Santa Bárbara, Ciudad Real	Mª Pilar Mur Gimeno

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Table 5. Autonomous communities in which the Alergodata Registry was filed or evaluated

Andalusia
Aragon
Castilla La Mancha
Castile and Leon
Catalonia
Canary Islands
Cantabria
Extremadura
Galicia
Madrid
Murcia
Basque Country
Valencia

The favorable opinion of 62 RECs was obtained, and contracts were signed with each of the 61 participating centers. In November 2021, access to the Alergodata Registry was opened, allowing the inclusion of patients who initiated biological treatment (or without biological treatment in the case of severe asthma) as of January 1, 2021. The electronic CRF (eCRF) is accessed via a URL address from any device, and each investigator has a site and investigator identification code. Researchers at the same facility can view and modify patient data from their site, maintaining data management traceability at all times. When the investigator enters a patient, the system provides a patient code. Only the investigator knows the patient's identification, and a confidential record must be maintained independently of the system and correlates the patient's data with the system code. That allows the investigator to enter follow-up visits for the same patient over time. This information is only known by the study team and should not leave the hospital at any time, as the patient data is coded, and only the research team may know the identity of the patients.

In the Alergodata Registry, a principal investigator was nominated for each center as the investigator responsible for the study in that center. Each center must assign one responsible investigator for each disease under study. Thus, some centers have only one researcher responsible for the four study diseases, while others have two, three, or four investigators responsible for coordination tasks for the different diseases, depending on how they are distributed. Table 6 lists the total number of researchers participating in the Alergodata Registry and the disease for which they are responsible. Two investigators cannot be responsible for one disease.

ETHICS AND DISSEMINATION

Following the Alergodata Registry protocol approved by the REC of the Hospital Clinic de Barcelona, the study is usually conducted at all times per the signed site contracts and in full compliance with the ethical guidelines for studies of this type, both in terms of providing information to the patient and requesting their informed consent for the ongoing follow-up and

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analysis of their clinical variables. Likewise, the clinical and technical supervision of the study ensures that routine clinical practice conditions will be respected: no variables will be collected that might identify the patients, and appropriate procedures to safeguard their confidentiality will be followed at all times.

The results of this study will be published primarily in scientific journals, authored by the members of the scientific committee and the physicians responsible for each disease in the centers, based on the merits guidelines agreed upon prior to the start of the registry. After the initial publication of the global study data, the communication of partial data may be authorized. SEAIC reserves the right to authorize the publication of individual data or sub-analyses. SEAIC will determine the most suitable policy for disseminating results to provide better patient care.

DISCUSSION

Few randomized controlled trials with a low risk of bias have provided direct, consistent information and objective evidence on treating complex chronic patients, such as those generally included in the Alergodata registry. The recommendations of the reference guidelines are usually based on indirect evidence from studies conducted on selected patients. This often results in inaccurate estimates for which, ideally, more controlled studies would be required. However, in the real world, it is clear that tools for ongoing observation and the agile analysis of day-to-day clinical practice would allow prospective studies to focus on the decision-making of our experts and real-world health outcomes as they occur [12]. In this changing world of information overload, decision-making cannot yet be categorically defined by evidence-based medicine, so it must be guided using analytical approaches based on the experience observed by specialists in each specific healthcare field to avoid variabilities in clinical and therapeutic practices that generate confounding factors in the management of already complex chronic patients.

Leading international institutions in the asthma study, such as the European Respiratory Society (ERS)/American Thoracic Society (ATS), have pointed to the need to join forces to improve the conditions of patients with severe asthma, a group recognized as an unmet need. Severe asthma is a heterogeneous condition expressed in various complex phenotypes, so coordinated analytical strategies in research are recommended to foster more specific and personalized diagnoses using safe and effective biomarkers [12, 28, 29]. Other holistic aspects benefit from the sentinel surveillance of these allergic diseases. For example, the evidence obtained from multiple epidemiological, pathophysiological, and therapeutic studies on the association between rhinitis and asthma [30-34] revealed that the prevalence of asthma in patients with allergic rhinitis is much higher than in the general population (< 2 %), and is even higher if we take into account subtypes of rhinitis, such as nasal polyposis that is associated with more severe asthma [35, 36]. The mechanisms for these phenomena are unknown, but the importance of a comprehensive approach to the study of treatments to gain more effective outcomes and disease control is well recognized [37-42]. In the case of atopic dermatitis, it is also essential to recognize that while dermatological therapeutic strategies are aimed at specific skin treatments and symptoms and diseases that affect certain areas, future research should also explore the "patient experience" because this can determine the particular symptom, location, and

response that is most important for the patient. These factors require ongoing sentinel surveillance of the different therapeutic strategies [43]. Overdiagnosis of urticaria remains a common reason for consultation in primary care centers, which the patient attends because of symptoms affecting their quality of life and work activity. It is imperative to underline the usefulness of instruments such as the diagnostic-therapeutic algorithm for acute and chronic urticaria, published in 2009 and updated in 2013, that structured decision-making based on differential diagnoses, thus optimizing the use of resources [44, 45]. In clinical practice, urticaria is a disease subject to a wide range of decisions requiring a more orderly criteria-based intervention. For this reason, the new guidelines recommend avoiding the systematic use of additional testing in acute urticaria, performing a complete blood count with ESR, and discontinuing NSAIDs (these compounds produce exacerbations in 20%-30% of patients) only in chronic cases. Diagnostic tests should only be requested if the patient presents symptoms suggestive of other associated diseases. It should be noted that most chronic urticaria is not allergic, so routine allergy testing is usually unnecessary. It is essential to underline the therapeutic foundations of urticaria, that is, the avoidance of triggers and aggravating factors and using pharmacological treatment (non-sedative antihistamines and new-generation drugs).

The management of these diseases, urticaria excepted, is often associated with underdiagnosis. In all of them, there is a great need to improve the use of treatments, foster a greater level of experience in primary care, and educate patients and family members to recognize warning symptoms. It is, therefore, essential to observe and act on all the factors involved, as far as possible, including patients and their environment. Awareness and health education must be promoted to correct avoidable behaviors, avoid unnecessary costs, and implement available treatment patterns more efficiently. In short, the SEAIC initiative is fully justified, given the need to extract all these scenarios from real-life experience and to analyze and act upon them, to re-analyze them periodically while considering and weighing up at all times the decision-making framework offered by evidence-based medicine.

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Table 6. Hospitals and researchers participating in the Alergodata Registry

Center ID	Work Center	Full name	Profile	Disease
1	Hospital Clínic de Barcelona	Antonio Valero	PI	Chronic rhinosinusitis
		Irina Bobolea	CI	Severe asthma
		Paula Ribó González	CI	Chronic urticaria and atopic dermatitis
2	Hospital Universitari Vall d'Hebron, Barcelona	Anna Sala Cunill	PI	Atopic dermatitis
		Olga Luengo Sanchez	CI	Severe asthma
		Moisés Labrador Horrillo	CI	Chronic urticaria
		Victoria Cardona Dahl	CI	Chronic rhinosinusitis
3	Hospital Universitari de Bellvitge, Barcelona	Mª Teresa Dordal Culla	PI	Severe asthma and chronic rhinosinusitis
		Jaume Marti Garrido	CI	Chronic urticaria and atopic dermatitis
4	Hospital Universitario Germans Trias i Pujol, Barcelona	Albert Roger Reig	PI	Chronic rhinosinusitis
		María Basagaña Torrentó	CI	Severe asthma
		Nathalie Depreux Niño	CI	Chronic urticaria
		Yanina Jurgens	CI	Atopic dermatitis
5	Hospital Sant Joan de Deu, Barcelona	Jaime Lozano Blasco	PI	Severe asthma
		Olga Domínguez Sánchez	CI	Chronic urticaria
		Carolina Prat Torres	CI	Atopic dermatitis
6	Consorci Sanitari de Terrassa, Barcelona	Marta Viñas Domingo	PI	Atopic dermatitis
		Nora Hernández Arauzo	CI	Severe asthma
		Adriana Izquierdo Domínguez	CI	Chronic rhinosinusitis
		Mª del Pilar Saura Foix	CI	Chronic urticaria
7	Hospital de Sant Joan de Déu de Manresa, Barcelona	Lidia Farrarons Lorente	PI	Severe asthma and chronic rhinosinusitis
		Natalia Magali Gímenez Licitra	CI	Chronic urticaria and atopic dermatitis
8	Hospital Santa Maria de Lleida	Lluis Marqués Amat	PI	Severe asthma
		María Peña Pelache	CI	Chronic rhinosinusitis
		Silvia Irene Corrales Vargas	CI	Chronic urticaria
9	Hospital Universitari Joan XXIII de Tarragona	Gaspar Dalmau Duch	PI	Severe asthma, chronic rhinosinusitis and atopic dermatitis
10	Hospital Universitario Ramón y Cajal, Madrid	Carmen Vidal Albareda	PI	Chronic urticaria
		David González de Olano	CI	Severe asthma
		Darío Antolín Amérigo	CI	Chronic rhinosinusitis
		Laura Carpio Escalona	CI	Atopic dermatitis
11	Hospital Universitario La Paz, Madrid	Santiago Quirce Gancedo	PI	Atopic dermatitis
		Pilar Barranco Sanz	CI	Severe asthma
		María Magdalena Lluch Bernal	CI	Chronic rhinosinusitis
		María Teresa Caballero Molina	CI	Chronic urticaria
12	Hospital Infantil Universitario Niño Jesús, Madrid	Sílvia Sánchez García	PI	Severe asthma
		Carmelo Escudero Díez	CI	Chronic urticaria
		Pablo Rodríguez del Río	CI	Atopic dermatitis
13	Hospital Universitario del Sureste, Madrid	Rafael Pineda Pineda	PI	Severe asthma and atopic dermatitis
		Beatriz Huertas Barbudo	CI	Chronic urticaria
		Mª Isabel Pérez Allegue	CI	Chronic rhinosinusitis
14	Hospital de Torrejón de Ardoz, Madrid	Armando Bueso Fernández	CI	Chronic rhinosinusitis
14	Hospital de Torrejón de Ardoz, Madrid	Alexandra Yago Meniz	CI	Chronic urticaria
14	Hospital de Torrejón de Ardoz, Madrid	Mª del Mar Goñi Yeste	CI	Chronic urticaria
15	Hospital Universitario Fundación Alcorcón, Madrid	Ana María Nieto Nieto	PI	Chronic urticaria
		Ana González Moreno	CI	Severe asthma
		Ana Rosado Ingelmo	CI	Chronic rhinosinusitis
		Mª Dolores Alonso Díaz de Durana	CI	Atopic dermatitis
16	Hospital Central de la Cruz Roja San José y Santa Adela, Madrid	Jose Julio Laguna Martinez	PI	Chronic rhinosinusitis
		Aranzazu Jimenez Blanco	CI	Severe asthma
		Maria Rosario Gonzalez Mendiola	CI	Chronic urticaria
		Cosmin Boteanu	CI	Atopic dermatitis
17	Hospital Universitario La Princesa de Madrid	Mª Victoria Múgica García	PI	Severe asthma and chronic rhinosinusitis
		Tania Ramos García	CI	Chronic urticaria and atopic dermatitis
18	CHUS-Complejo Hospitalario Universitario de Santiago, La Coruña	Virginia Rodriguez Vázquez	PI	Atopic dermatitis
		Paula Méndez Brea	CI	Severe asthma and chronic rhinosinusitis
		Sara López Freire	CI	Chronic urticaria
19	Complexo Hospitalario Universitario A Coruña	Antonio Parra Arrondo	PI	Chronic rhinosinusitis
		Beatriz Veleiro Pérez	CI	Chronic urticaria and atopic dermatitis
		Manuel Jorge Rial Prado	CI	Severe asthma
20	Hospital Da Costa Burela (Hospital Da Mariña), Lugo	Nicola Giangrande	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria, and atopic dermatitis

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Center ID	Work Center	Full name	Profile	Disease
21	Hospital Provincial de Pontevedra	Tania Liñares Mata	PI	Severe asthma and chronic rhinosinusitis
		María Teresa Soto Mera	CI	Chronic urticaria and atopic dermatitis
22	Hospital Meixoeiro, Vigo, Pontevedra	Angela Meijide Calderón	PI	Chronic urticaria
		Mónica Fernández Rodríguez	CI	Severe asthma
		Carmen Marcos Bravo	CI	Chronic rhinosinusitis
		Ana Rodríguez Fernández	CI	Atopic dermatitis
23	Hospital de Llíria, Valencia	Javier Montoro Lacomba	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
24	Hospital Universitario de La Ribera, Valencia	Juan José Liñana Santafé	PI	Chronic urticaria and atopic dermatitis
		Isabel Molero Sancho	CI	Severe asthma and chronic rhinosinusitis
25	Consorci Hospital General Universitari de Valencia	Maria Dolores de las Marinas Alvarez	PI	Chronic urticaria
		Marta Alvariño	CI	Severe asthma
		Juan Carlos Cerda Mir	CI	Chronic rhinosinusitis
		Cristina Martorell Calatayud	CI	Atopic dermatitis
26	Hospital Universitario Dr. Peset, Valencia	Carmen Pérez Francés	PI	Severe asthma
		Anna Ferrer Franco	CI	Chronic rhinosinusitis, chronic urticaria and atopic dermatitis
27	Hospital Universitario de la Plana, Villarreal, Castellón	David El-Qutob López	PI	Severe asthma and chronic rhinosinusitis
		María Nieto Cid	CI	Chronic urticaria and atopic dermatitis
28	Hospital Universitario del Vinalopó, Elche, Alicante	Mónica Antón Gironés	PI	Chronic rhinosinusitis, atopic dermatitis and severe asthma
		Alejandra González Pérez	CI	Chronic urticaria
29	Hospital Universitario de Torrevieja, Alicante	María Dolores Martos Calahorro	PI	Chronic urticaria and atopic dermatitis
30	Hospital Vega Baja, Orihuela, Alicante	Angel Ferrer Torres	PI	Severe asthma and chronic rhinosinusitis
		Carmen María Andreu Balaguer	CI	Chronic urticaria and atopic dermatitis
32	Hospital HLA Jerez Puerta del Sur, Jerez de la Frontera, Cádiz	Antonio Letrán Camacho	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
33	Hospital Universitario Virgen Macarena, Seville	Pedro Guardia Martinez	PI	Atopic dermatitis
		Julio Delgado Romero	CI	Severe asthma
		Carmen Segura Sánchez	CI	Chronic rhinosinusitis
		Maria Cesárea Sánchez Hernández	CI	Chronic urticaria
34	Hospital Universitario Virgen del Rocío, Seville	Robledo Ávila Castellano	PI	Chronic urticaria and chronic rhinosinusitis
		Stefan Cimbollek	CI	Severe asthma and atopic dermatitis
36	Hospital Materno Infantil HRU de Málaga	Candelaria Muñoz Román	PI	Severe asthma, atopic dermatitis and chronic urticaria
37	Hospital Regional Universitario Carlos Haya/Hospital Regional Universitario de Málaga	José María Vega Chicote	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
38	Hospital Universitario de Jaén	Manuel Alcantara Villar	PI	Chronic urticaria
		Carmen Laura Cañada Peña	CI	Atopic dermatitis
		Mª Antonia Navarrete del Pino	CI	Chronic rhinosinusitis
39	Hospital QuironSalud Córdoba	Ignacio García Núñez	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
40	Hospital Universitario Clínico San Cecilio, Granada	J. Fernando Florido López	PI	Atopic dermatitis
		Carolina Mérida Fernández	CI	Chronic rhinosinusitis
		Mª Ángeles Lara Jiménez	CI	Chronic urticaria
		María José Rojas Vílchez	CI	Severe asthma
41	Hospital HLA Inmaculada, Granada	Isabel Fernández de Alba Porcel	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
42	Hospital Clínico Universitario Lozano Blesa, Zaragoza	Juan Fraj Lázaro	PI	Severe asthma
		José Luis Cubero Saldaña	CI	Chronic rhinosinusitis
		Mª del Mar Garcés Sotillos	CI	Atopic dermatitis
		Apolinar Lezaun Alfonso	CI	Chronic urticaria

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Center ID	Work Center	Full name	Profile	Disease
43	Hospital Universitario Cruces, Vizcaya	Ignacio Jáuregui	PI	Chronic urticaria and atopic dermatitis
		Pedro M. Gambon Setien	CI	Severe asthma
		Mª Dolores Martinez Anton	CI	Chronic rhinosinusitis
44	Hospital Universitario Donostia, Guipúzcoa	Susana Lizarza Mendizabal	PI	Chronic urticaria
		Jose Antonio Navarro Echeverria	CI	Severe asthma and chronic rhinosinusitis
		Alejandro Joral Badas	CI	Atopic dermatitis
45	Hospital Universitario de Araba, Álava	Eduardo Fernández Ibañez	PI	Severe asthma
		Maria Teresa Audicana Berasategi	CI	Chronic urticaria
		Olga Villarreal Balza de Vallejo	CI	Atopic dermatitis
		Marta Velasco Azagra	CI	Chronic rhinosinusitis
46	Complejo Asistencial de Zamora	José Camilo Martínez Alonso	PI	Severe asthma
		Milagros Lázaro Sastre	CI	Atopic dermatitis and chronic rhinosinusitis
		Ana María Callejo Melgosa	CI	Chronic urticaria
47	Hospital Universitario de Burgos	Pedro Carretero Anibarro	PI	Atopic dermatitis
		Laura Manzanedo Ortega	CI	Severe asthma
		Reyes Pérez Gimenez	CI	Chronic urticaria
		Patricia Alloza Gomez	CI	Chronic rhinosinusitis
49	Hospital El Bierzo, León	Beatriz Fernández Parra	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
50	Hospital General Rio Carrión, Palencia	Susana Cabrerizo Ballesteros	PI	Severe asthma and atopic dermatitis
		María Isabel Garcimartin Galicia	CI	Chronic urticaria
51	Hospital Universitario de Salamanca	Ignacio Jesús Dávila González	PI	Severe asthma
		Francisco Javier Muñoz Bellido	CI	Chronic urticaria
		Maria Gil Melcón	CI	Chronic rhinosinusitis
		Cristina Martin García	CI	Atopic dermatitis
52	Hospital Virgen del Valle, Toledo	Isabel María Sánchez Matas	PI	Chronic urticaria and atopic dermatitis
		Mª del Mara Moro Moro	CI	Severe asthma
		Mª Mar Jiménez Lara	CI	Chronic rhinosinusitis
53	Hospital Nuestra Señora del Prado de Talavera de la Reina, Toledo	Álvaro Moreno Ancillo	PI	Severe asthma
		Jesús Jurado Palomo	CI	Atopic dermatitis
		Magdalena Julia Caminoa Irisarri	CI	Chronic urticaria
		Carmen Panizo Bravo	CI	Chronic rhinosinusitis
54	Hospital General Universitario Ciudad Real	Pedro Galindo Bonilla	PI	Severe asthma
		Francisco Feo Brito	CI	Chronic rhinosinusitis
		Jesús Mª Borja Segade	CI	Chronic urticaria
		María Aranzazu Martín Iglesias	CI	Atopic dermatitis
55	Hospital General de Villarrobledo, Albacete	Ana Montoro Ferrer	PI	Severe asthma, chronic rhinosinusitis, chronic urticaria and atopic dermatitis
56	Complejo Hospitalario Universitario Albacete	Patricia Prieto Montaño	PI	Severe asthma
		Maria Teresa Asensio Sánchez	CI	Chronic urticaria
58	Hospital Ciudad de Coria, Cáceres	Beatriz Hierro Santurino	PI	Chronic urticaria
59	Complejo Hospitalario de Mérida, Badajoz	Alicia Habernau Mena	PI	Severe asthma and chronic rhinosinusitis
		Rafael Aragón López	CI	Chronic urticaria and atopic dermatitis
60	Hospital Universitario de Badajoz	M. Ángeles Gonzalo Garijo	PI	Chronic rhinosinusitis
		Gloria Jiménez Ferrera	CI	Chronic urticaria
		Remedios Pérez Calderón	CI	Severe asthma
		Jesús Miguel García Menaya	CI	Atopic dermatitis
62	Complejo Universitario Insular Materno infantil de Gran Canaria, Las Palmas	Dara Martínez Beltran	PI	Severe asthma and chronic rhinosinusitis
		Raquel Cabrera Hernández	CI	Chronic urticaria and atopic dermatitis
63	Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife	Ruperto González Pérez	PI	Severe asthma and chronic rhinosinusitis
		Paloma Poza Guedes	CI	Chronic urticaria and atopic dermatitis
64	Hospital General Universitario Morales Meseguer, Murcia	Ana Mora Gonzalez	PI	Severe asthma
		Laura Victorio Puche	CI	Chronic urticaria
		Ana Martínez Navarro	CI	Chronic rhinosinusitis
65	Hospital Universitario Rafael Méndez, Murcia	Sheila Cabrejos Perotti	PI	Chronic rhinosinusitis and atopic dermatitis
		Geiny Cabel Diaz Defrank	CI	Severe asthma and chronic rhinosinusitis
66	Hospital Público Santa Bárbara, Ciudad Real	Mª Pilar Mur Gimeno	PI	Severe asthma and chronic rhinosinusitis
		Alba María Extremera Ortega	CI	Chronic urticaria

CI, co-investigator; PI, principal investigator.

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REFERENCES

1. Escarrer-Jaume M, Juliá-Benito JC, Quevedo-Teruel S, Prieto del-Prado A, Sandoval-Ruballos M, Quesada-Sequeira F, et al. Cambios en la epidemiología y en la práctica clínica de la alergia mediada por IgE en pediatría. Anales de pediatria. 2021;95(1):56.e1-.e8.
2. The European Academy of Allergy and Clinical Immunology (EAACI). Advocacy Manifesto. Tackling the allergy crisis in Europe-Concerted policy action needed. 2015.
3. Zubeldia JMB, L; Chivato, T; Jáuregui, I; Senent, C.J. El libro de las enfermedades alérgicas. Bilbao: Fundación BBVA; 2021.
4. Saco TV, Pepper A, Casale TB. Uses of Biologics in Allergic Diseases: What to Choose and When. Annals of Allergy, Asthma & Immunology. 2018;120(4):357-66.
5. Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A, et al. EAACI IG Biologicals Task Force Paper on the Use of Biologic Agents in Allergic Disorders. Allergy. 2015;70(7):727-54.
6. Tan HT, Sugita K, Akdis CA. Novel Biologicals for the Treatment of Allergic Diseases and Asthma. Current allergy and asthma reports. 2016;16(10):70.
7. Eyerich S, Metz M, Bossios A, Eyerich K. New Biological Treatments for Asthma and Skin Allergies. Allergy. 2019;75(3):546-60.
8. Kim HS, Lee S, Kim JH. Real-world Evidence Versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. Journal of Korean medical science. 2018;33(34):e213.
9. The Association of British Pharmaceutical Industry (ABPI). Demonstrating value with real world data: A practical guide. 2011.
10. European Medicines Agency. EMA patient registries initiative - Strategy and Mandate of the Cross-Committee Task Force. 2017.
11. McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, et al. Patient Registries: An Underused Resource for Medicines Evaluation : Operational Proposals for Increasing the Use of Patient Registries in Regulatory Assessments. Drug safety. 2019;42(11):1343-51.
12. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. The European respiratory journal. 2014;43(2):343-73.
13. Comité Ejecutivo de la GEMA. GEMA 4.4 - Guía española para el manejo del asma. Sociedad Española de Médicos Generales y de Familia (SEMG),2019.
14. Alobid I, Antón E, Armengot M, Chao J, Colás C, del Cuvillo A, et al. SEAIC-SEORL. Consensus Document on Nasal Polyposis. POLINA Project. Journal of investigational allergology & clinical immunology. 2011;21 Suppl 1:1-58.
15. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, Akerlund A, et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. Allergy. 2004;59(4):406-14.
16. Hollis K, Proctor C, McBride D, Balp M-M, McLeod L, Hunter S, et al. Comparison of Urticaria Activity Score Over 7 Days (UAS7) Values Obtained From Once-Daily and Twice-Daily Versions: Results From the ASSURE-CSU Study. American journal of clinical dermatology. 2018;19(2):267-74.
17. García-Díez I, Curto-Barredo L, Weller K, Pujol RM, Maurer M, Giménez-Arnau AM. Cross-Cultural Adaptation of the Urticaria Control Test From German to Castilian Spanish. Actas dermo-sifiliograficas. 2015;106(9):746-52.

18. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014;133(5):1365-72, 72.e1-6.
19. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol. 2007;157(4):645-8.
20. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. The Journal of dermatological treatment. 2015;26(1):23-31.
21. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140(12):1513-9.
22. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. The European respiratory journal. 1999;14(1):32-8.
23. Khan AH, Reaney M, Guillemin I, Nelson L, Qin S, Kamat S, et al. Development of Sinonasal Outcome Test (SNOT-22) Domains in Chronic Rhinosinusitis With Nasal Polyps. The Laryngoscope. 2022;132(5):933-41.
24. Levy JM, Mace JC, Rudmik L, Soler ZM, Smith TL. Low 22-item sinonasal outcome test scores in chronic rhinosinusitis: Why do patients seek treatment? The Laryngoscope. 2017;127(1):22-8.
25. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy. 2005;60(8):1073-8.
26. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clinical and experimental dermatology. 1994;19(3):210-6.
27. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132(6):942-9.
28. Dávila I, Quirce S, Olaguibel JM. Selection of Biologics in Severe Asthma: A Multifaceted Algorithm. Journal of investigational allergology & clinical immunology. 2019;29(4):325-8.
29. Quirce S, Bobolea I, Domínguez-Ortega J, Barranco P. Future biologic therapies in asthma. Arch Bronconeumol. 2014;50(8):355-61.
30. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
31. Navarro A, Colas C, Anton E, Conde J, Davila I, Dordal MT, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergologica-2005. Journal of investigational allergology & clinical immunology. 2009;19 Suppl 2:7-13.
32. Valero A, Pereira C, Loureiro C, Martinez-Cocera C, Murio C, Rico P, et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: a study of Spain and Portugal. Journal of investigational allergology & clinical immunology. 2009;19(3):167-72.
33. del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients - The ADRIAL cohort study. Rhinology. 2010;48(2):201-5.
34. Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004;113(1):86-93.
35. de Llano LP, Vennera Mdel C, Álvarez FJ, Medina JF, Borderías L, Pellicer C, et al. Effects of omalizumab in non-atopic asthma: results from a Spanish multicenter registry. J Asthma. 2013;50(3):296-301.

36. Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, et al. Association between severity of asthma and degree of chronic rhinosinusitis. Am J Rhinol Allergy. 2011;25(4):205-8.
37. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008;372(9643):1049-57.
38. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. Allergy. 2008;63(3):292-8.
39. de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. Thorax. 2012;67(7):582-7.
40. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. BMC pulmonary medicine. 2006;6 Suppl 1:S3.
41. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. J Asthma. 2006;43(1):1-7.
42. Oka A, Matsunaga K, Kamei T, Sakamoto Y, Hirano T, Hayata A, et al. Ongoing allergic rhinitis impairs asthma control by enhancing the lower airway inflammation. J Allergy Clin Immunol Pract. 2014;2(2):172-8.
43. Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. The patient. 2019;12(5).
44. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69(7):868-87.
45. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy. 2009;64(10):1417-26.

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