

Establishment and Utility of SwedAD: A Nationwide Swedish Registry for Patients with Atopic Dermatitis Receiving Systemic Pharmacotherapy

Mikael ALSTERHOLM^{1,2}, Axel SVEDBOM², Chris D. ANDERSON^{3,4}, Lena HOLM SOMMAR⁵, Lina U. IVERT^{2,6}, Anna JOSEFSON^{7,8}, Laura von KOBLETZKI^{7,9}, Magnus LINDBERG⁷, Lena LUNDEBERG^{2,6}, Maria LUNDQVIST^{2,6}, Elisabet NYLANDER¹⁰, MariHelen SANDSTRÖM FALK¹¹, Alexander SHAYESTEH¹⁰, Gunnthorunn SIGURDARDOTTIR³, Andreas SONESSON^{12,13}, Åke SVENSSON^{9,12}, Marie VIRTANEN¹⁴, Sophie VRANG¹⁵, Carl-Fredrik WAHLGREN², Maria BRADLEY^{2,6#} and Emma K. JOHANSSON^{2,6#}

¹Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, ²Dermatology and Venereology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, ³Department of Dermatology and Venereology, County Council of Östergötland, Linköping, ⁴Department of Biomedical and Clinical Sciences. Division of Cell Biology, Linköping University, Linköping, ⁵Stockholm Hud, Stockholm, ⁶Department of Dermatology and Venereology, Karolinska University Hospital, Stockholm, ⁷School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, ⁸Department of Dermatology, University Hospital Örebro, Örebro, ⁹Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö, ¹⁰Department of Public Health and Clinical Medicine, Dermatology and Venereology, Umeå University, Umeå, ¹¹Capio Skin, Carlanderska Hospital, Gothenburg, ¹²Department of Dermatology and Venereology, Skåne University Hospital, Lund, ¹³Division of Dermatology and Venereology, Clinical Sciences, Lund University, Lund, ¹⁴Department of Medical Sciences, Section of Dermatology, Uppsala University, Uppsala and ¹⁵Patients' organization Atopikerna, The Swedish Asthma and Allergy Association, Stockholm, Sweden
#These authors contributed equally.

SwedAD, a Swedish nationwide registry for patients with atopic dermatitis receiving systemic pharmacotherapy, was launched on 1 September 2019. We describe here the establishment of a user-friendly registry to the benefit of patients with atopic dermatitis. By 5 November 2022, 38 clinics had recorded 931 treatment episodes in 850 patients with an approximate national coverage rate of 40%. Characteristics at enrolment included median Eczema Area and Severity Index (EASI) 10.2 (interquartile range 4.0, 19.4), Patient-Oriented Eczema Measure (POEM) 18.0 (10.0, 24.0), Dermatology Life Quality Index (DLQI) 11.0 (5.0, 19.0) and Peak Itch Numerical Rating Scale-11 (NRS-11) 6.0 (3.0, 8.0). At 3 months, median EASI was 3.2 (1.0, 7.3) and POEM, DLQI, and NRS-11 were improved. Regional coverage varied, reflecting the distribution of dermatologists, the ratio of public to private healthcare, and difficulties in recruiting certain clinics. This study highlights the importance of a nationwide registry when managing systemic pharmacotherapy of atopic dermatitis.

Key words: dupilumab; Janus kinase inhibitors; methotrexate; real-world data; registries.

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Corr: Mikael Alsterholm, Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, SE-413 45 Gothenburg, Sweden. E-mail: mikael.alsterholm@gu.se

Atopic dermatitis (AD) is a relapsing inflammatory skin disease characterized by skin dryness, scratching, and itchy red rash that favours flexural areas and the face. Individuals with AD experience itch, sleep disturbance, and skin lesions that affect social interaction

SIGNIFICANCE

SwedAD, a recently initiated Swedish nationwide quality registry for patients with atopic dermatitis, demonstrates the effectiveness of conventional and new systemic pharmacotherapy on clinical signs and symptoms. A well-designed quality registry is a helpful tool for patients and clinicians to achieve standardized evaluation of treatment for individual agents and over time. It allows clinicians and researchers to monitor efficacy and side-effects for different therapies and can aid in the planning and decision-making of clinicians and healthcare authorities.

and health-related quality of life (1, 2). While topical anti-inflammatory drugs and ultraviolet (UV) phototherapy can often manage the disease, approximately 2% of patients have recalcitrant AD, which does not respond to this regimen and requires a variety of systemic immunosuppressive or antimicrobial treatments in combination or sequentially (3, 4). Recently, several new systemic treatments for AD; monoclonal antibodies dupilumab and tralokinumab and Janus kinase (JAK) inhibitors baricitinib, upadacitinib, and abrocitinib, have been introduced. Additional systemic treatments are expected to be registered in the near future. This has highlighted the importance of structured follow-up of patient- and investigator-reported outcome measures to monitor efficacy and safety beyond randomized clinical trials. A quality registry is an established way of achieving this real-world data.

The variables in a quality registry should be relevant for users and allow for comparability and pooling of data in collaborations with other registries. There are several initiatives to define and implement the use of appropriate outcome measures. Harmonising Outcome Measures for Eczema (HOME) recommends variables

for clinical trials and monitors their adoption in the research community (5–7). The TREATment of Atopic Eczema Registry Taskforce (TREAT) has established a core dataset for registries based on the recommendations from HOME and others (8, 9).

The new systemic AD treatments have been evaluated in clinical trials on selected patients, but real-life data is still scarce. Therefore, it is important to collect data prospectively and systematically as we implement these new treatments in clinical care (10, 11). Conventional systemic treatments for AD are used based on accumulated clinical experience. In many cases prescription is off-label and, within this group of pharmaceuticals, there is also a paucity of follow-up data.

In this setting, the process of establishing a Swedish registry for patients with AD receiving systemic pharmacotherapy is described. Considerations regarding the choice of outcome variables, interface design and launching, as well as post-launching challenges, are presented. Coverage rate and data at baseline and follow-up for selected outcome measures are demonstrated.

MATERIALS AND METHODS

Initiative and organization

In 2017, a local registry for patients with AD receiving systemic treatment was started at Karolinska University Hospital, Stockholm. The registry was intended as a tool for clinical follow-up, decision-making, and research. The registry was soon digitized on a technical platform provided by Carmona (Halmstad, Sweden), a company specialized in software for healthcare registries.

In early 2018, dermatologists from Sweden's 7 medical university faculties met to discuss the national harmonization of treatment and follow-up for moderate to severe AD. In view of the anticipated rapid development of new drugs for AD it was decided that a nationwide quality registry for patients with AD receiving systemic pharmacotherapy was the best option for patients, clinicians, and researchers. Such a registry would monitor treatment effects, side-effects, aid clinical decision-making, facilitate research, and provide data for the decisions of healthcare authorities. A steering group for the proposed quality registry was formed by the assembled representatives and subsequently joined by dermatologists from private healthcare and the chairperson of the patients' organization for AD. The registry was named SwedAD, an abbreviation of Sweden Atopic Dermatitis. The steering group consists of the authors of this paper.

SwedAD was based on the local registry at Karolinska University Hospital, modified to meet the requirements of a quality registry. The steering group held consensus meetings at regular intervals to decide on relevant outcome measures, variables, and software interface design. In the planning stage, the steering group consulted QRC Stockholm, a regional and national centre for quality registries. QRC Stockholm offered advice on development and launching and helped to ensure that SwedAD was compliant with the rules and regulations for a quality registry. Based on the recommendation that all quality registries in Sweden should belong to a regional registry centre, SwedAD is affiliated with QRC Stockholm. Karolinska University Hospital was chosen as central personal data controller.

Registration of outcome measures

Carmona provided the digital platform for the registry and designed the interface according to specifications from the steering group. SwedAD is digitally accessed, for patients and clinicians, via a website (www.swedad.nu), which was set up and is maintained by the registry managers' work group. In addition to the log-in portal, the website contains information about SwedAD for users.

The selection of outcome variables was based mainly on the recommendations by HOME and the core outcome set adopted by the registries in the TREAT Registry Taskforce (5, 8, 9, 12, 13).

Data are collected at each patient visit. Frequency of visits is according to the clinician's assessment and local routine. Compulsory investigator-reported outcome measures collected are Eczema Area and Severity Index (EASI) or the children's version (cEASI) for patients <8 years of age, blood pressure, body weight, any change in systemic treatment, and any side-effect leading to termination of treatment (14). Patient-reported outcome measures (PROMs) are Dermatology Life Quality Index (DLQI) or the children's version (CDLQI) for patients between 4 and 15 years of age, Patient-Oriented Eczema Measure (POEM), Peak Itch Numerical Rating Scale-11 (NRS-11), Montgomery-Åsberg Depression Rating Scale (MADRS-S) (age ≥ 16 years), and additional questions regarding emotional stressors (work, school, family, finance) (15–20). At enrolment, education level and data on atopic comorbidities of the patient and first-degree relatives are registered by the clinician. At 1 visit per year selected comorbidities and alcohol and smoking habits are entered.

To report PROMs and other variables, patients log in to SwedAD on their preferred device with electronic identification (mobile BankID). To obtain a BankID the person must have a Swedish personal identity number and be the customer of a bank that issues the identification. As of November 2020, 96.5% of Swedes aged 18–67 years were registered mobile BankID users (Statistics Sweden; SCB). Many individuals outside this age range are also users. Clinics may offer their patients to report PROMs on a reading tablet in the waiting room or ask them to use their own device, including smartphones, at any time prior to their appointments.

PROMs are downloaded by the clinician and presented in time-lined graphs and tables that can be shown to the patient at each visit. Investigator-reported outcome measures are put in during the visit or when convenient. To accommodate local preferences or research projects, the SwedAD interface provides the opportunity to register more variables than those defined as mandatory by the steering group.

Promotion and launching

SwedAD was promoted in the official publication of the Swedish Society of Dermatology and Venereology and through lectures given by members of the steering group leading up to the launch on 1 September 2019. On-site start-up meetings, led by members of the registry managers' work group, were held in clinics that were interested to join up, until the start of the COVID-19 pandemic, after which meetings were mainly digital. Promotional activities and local assistance with start-up are on-going. The registry coordinator is available for technical queries from participating clinics. Information for patients about SwedAD is distributed through the web site and social media of the patients' organization Atopikerna (<https://atopikerna.astmaoallergiforbundet.se>).

Maintenance and funding

The steering group convenes regularly to discuss the maintenance and development of SwedAD. Applications for data extraction from researchers are reviewed and granted or denied in accordance with the statutes of the registry.

Table I. Baseline and background characteristics at enrolment for patients in SwedAD

Characteristic	Data available n	
Age, years, mean (SD)	n = 850	41.9 (18.6)
Age distribution, n (%)	n = 850	
< 6 years		2 (0.2)
6–12 years		29 (3.4)
13–17 years		34 (4.0)
18–65 years		671 (78.9)
> 65 years		114 (13.4)
Sex, n (%)	n = 850	
Male		446 (52.5)
Female		404 (47.5)
BMI, kg/m ² , mean (SD)	n = 413	25.9 (6.1)
EASI, median (IQR)	n = 785	10.2 (4.0, 19.4)
cEASI, median (IQR)	n = 6 ^a	10.9 (3.2, 12.8)
POEM, median (IQR)	n = 755	18.0 (10.0, 24.0)
DLQI, median (IQR)	n = 728	11.0 (5.0, 19.0)
CDLQI, median (IQR)	n = 38 ^a	10.0 (5.0, 17.0)
NRS-11 itch, median (IQR)	n = 691	6.0 (3.0, 8.0)
Age at onset of AD, n (%)	n = 468	
< 2 years		237 (50.6)
2–6 years		133 (28.4)
7–12 years		34 (7.3)
13–19 years		10 (2.1)
≥ 20 years		54 (11.5)
Allergic rhinoconjunctivitis, n (%)	n = 478	382 (79.9)
Asthma, n (%)	n = 470	246 (52.3)
Current smoker, n (%)	n = 493	71 (14.4)
Current snuff user, n (%)	n = 498	83 (16.7)
Diabetes, n (%)	n = 509	23 (4.5)
Myocardial infarction, n (%)	n = 507	14 (2.8)
Stroke, n (%)	n = 506	11 (2.2)
Highest level of education, n (%)	n = 439	
Elementary school		38 (8.7)
High school		173 (39.4)
Other post-secondary education		25 (5.7)
University < 3 years		57 (13.0)
University ≥ 3 years		140 (31.9)
None of the above		6 (1.4)

^aChildren Eczema Area and Severity Index (cEASI) is used for patients < 8 years and Children Dermatology Life Quality Index (CDLQI) is used for patients aged 4–15 years.

BMI: body mass index; EASI: Eczema Area and Severity Index; POEM: Patient-Oriented Eczema Measure; NRS-11: Peak Itch Numerical Rating Scale-11; DLQI: Dermatology Life Quality Index; AD: atopic dermatitis.

The university dermatology departments share the cost of technical maintenance of SwedAD, which is provided by Carmona. Participation is free of charge for all other clinics. The working hours for the members of the steering group are mainly funded by their respective research grants and employers. The steering group continuously applies for relevant grants for research projects and the registry itself. Annual reports with selected data from SwedAD have been offered to pharmaceutical companies for a fee.

Statistical analysis

Background characteristics were expressed as a percentage of the total number of individuals observed. For baseline outcomes, the first observed value for each patient was selected and presented as median value and interquartile range (IQR). Enrolment rate by county was given as the number of patients in SwedAD per 100,000 inhabitants. The number of treatments stratified by drugs were presented as a percentage of total treatment episodes that were on-going at enrolment or started later. Longitudinal data were based on treatment episodes, i.e. 1 included patient could have provided multiple data if the patient had experienced more than 1 treatment episode during follow-up. Drug survival was estimated using Kaplan–Meier methodology, all drugs together. Treatment episodes were censored at the earliest of: (i) 180 days after the latest registered visit, and (ii) date of data extraction.

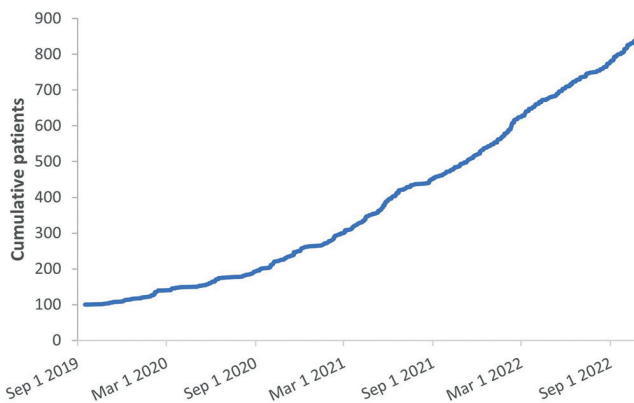


Fig. 1. Progression of enrolment in SwedAD from 1 September 2019 to 5 November 2022. At the launch of SwedAD, 100 patients from the local registry at Karolinska University Hospital were already enrolled.

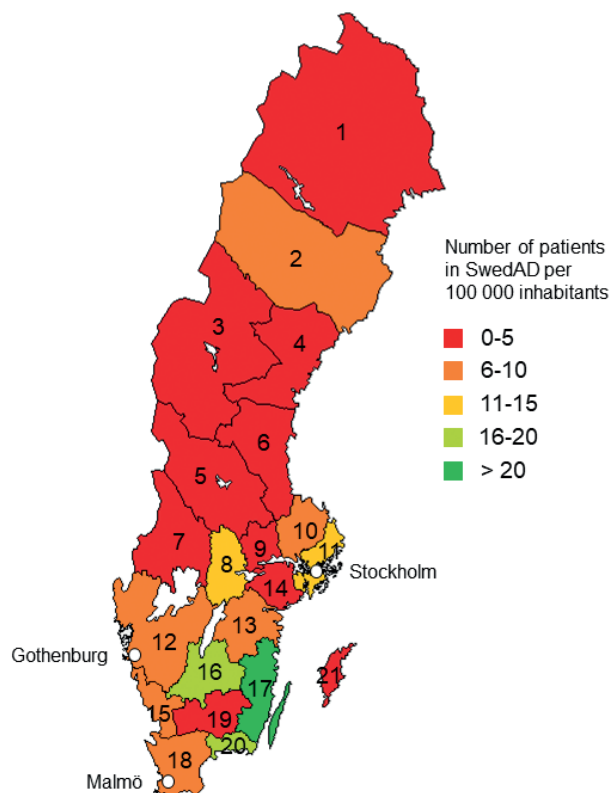


Fig. 2. Geographical distribution of enrolment in SwedAD. Number of patients enrolled in SwedAD per 100,000 inhabitants for each county in Sweden on 5 November 2022. 1: Norrbotten County; 2: Västerbotten County; 3: Jämtland County; 4: Västermorrland County; 5: Dalarna County; 6: Gävleborg County; 7: Värmland County; 8: Örebro County; 9: Västmanland County; 10: Uppsala County; 11: Stockholm County; 12: Västra Götaland County; 13: Östergötland County; 14: Södermanland County; 15: Halland County; 16: Jönköping County; 17: Kalmar County; 18: Skåne County; 19: Kronoberg County; 20: Blekinge County; 21: Gotland County.

All statistical calculations were performed with Stata statistical software (release 17.2; StataCorp, College Station, TX, USA).

RESULTS

Patients of any age with AD according to the UK Working Party's Diagnostic Criteria, receiving systemic pharmacotherapy were eligible for enrolment (21). Systemic pharmacotherapy was defined as 1 or more oral or subcutaneous drugs prescribed for AD. Baseline characteristics for enrolled patients are shown in **Table I**.

The number of participating clinics and patients increased rapidly (**Fig. 1**). At the launch, 100 patients from the local registry at Karolinska University Hospital, Sweden, were already enrolled. By 5 November 2022, 931 treatment episodes in 850 patients from 38 clinics were registered. A treatment episode was defined as 1 specified systemic pharmacotherapy used continuously by 1 patient, either ongoing at enrolment or started after enrolment. The number of enrolled patients per 100,000 inhabitants varied over the 21 counties of Sweden (**Fig. 2**).

Dupilumab was the most widely prescribed treatment, with 566 episodes (61.0%), followed by methotrexate, accounting for 256 episodes (27.5%). The distribution

Table II. Distribution of systemic pharmacotherapy for patients with atopic dermatitis in SwedAD from 1 September 2019 to 5 November 2022

Treatment, drug	Treatment episodes ^a (n = 931) n (%)
Alitretinoin ^b	2 (0.2)
Azathioprine	3 (0.3)
Baricitinib	22 (2.4)
Cyclosporine	51 (5.5)
Dupilumab	566 (61.0)
Mycophenolate mofetil	1 (0.1)
Methotrexate	256 (27.5)
Upadacitinib	30 (3.2)

^aA treatment episode was defined as 1 specified systemic pharmacotherapy used continuously by 1 patient, either ongoing at enrolment or started after enrolment.

^bAlitretinoin, which is usually considered a treatment option for hand eczema rather than atopic dermatitis, was registered for 2 treatment episodes.

of all systemic pharmacotherapies among all treatment episodes is shown in **Table II**. Most patients improved on treatment reflected in a median of EASI 12.0 (interquartile range 6.0, 20.8) at treatment start and 3.2 (1.0, 7.3) after 3 months. As for EASI, the median POEM, DLQI, and NRS-11 scores improved during follow-up (**Fig. 3**).

Drug survival was 71% at 1 year, i.e. 71% of all initiated treatment episodes were on-going by 1 year. At 2 years, 62% of all initiated treatment episodes were on-going (**Fig. 4**).

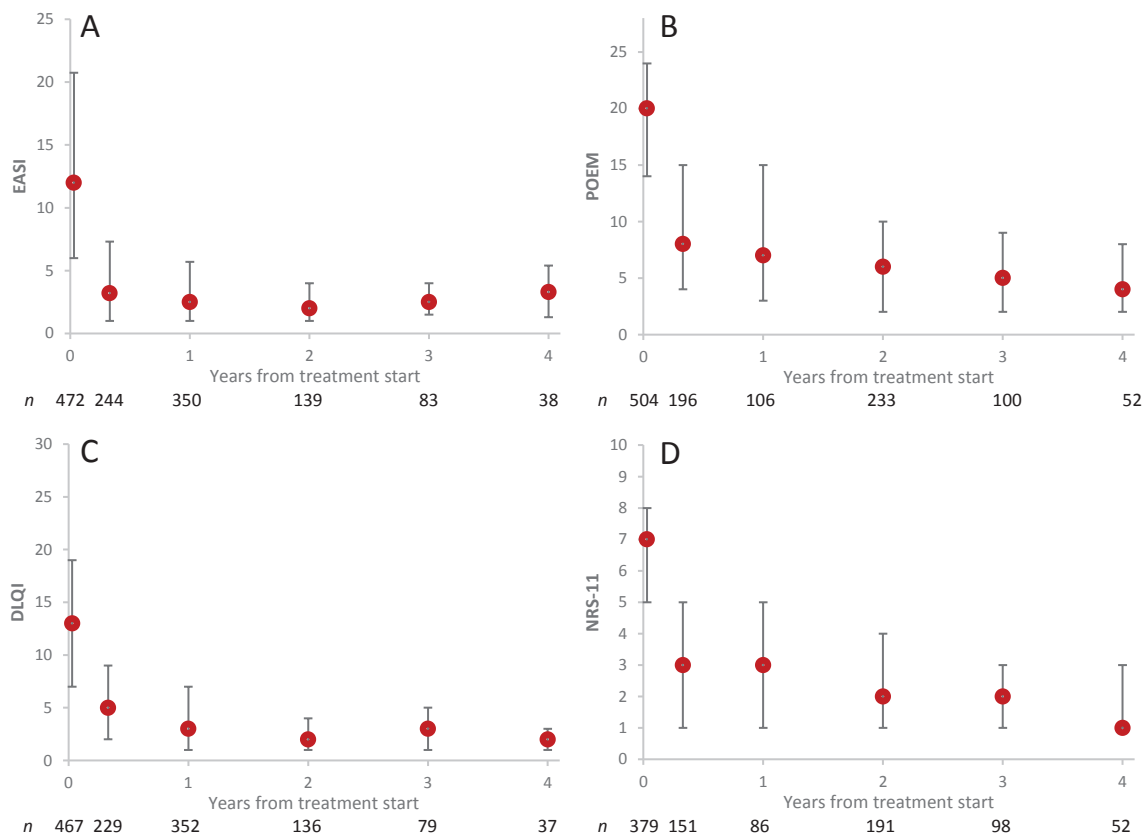


Fig. 3. Effect of systemic pharmacotherapy for atopic dermatitis (AD) on Eczema Area and Severity Index (EASI) and patient-reported outcome measures in SwedAD for all enrolled patients. All scores are presented at treatment start (within 30 days of start), at 120 days (\pm 30 days), and at 1, 2, 3, and 4 years (\pm 0.5 years each). Circle indicates the median for all observations in the relevant time period and the upper and lower bounds of the bar represent the interquartile range. (A) EASI. (B) Patient-Oriented Eczema Measure (POEM). (C) Dermatology Life Quality Index (DLQI). (D) Peak Itch Numerical Rating Scale-11 (NRS-11). Since a visual analogue scale was used for itch assessment prior to September 2019, such ratings are not included in the figure.

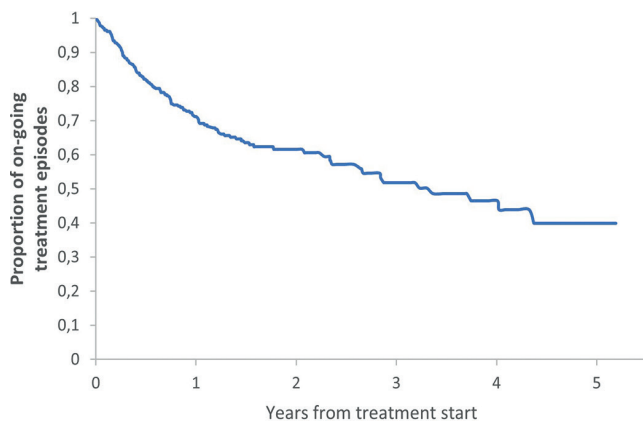


Fig. 4. Drug survival for systemic pharmacotherapy in SwedAD. Drug survival was estimated using Kaplan–Meier methodology. The displayed data includes all initiated treatment episodes for atopic dermatitis after enrolment. Enrolled patients can have 1 or more treatment episodes. The graph depicts the proportion of on-going treatment episodes at a given time-point after treatment start.

To estimate coverage rate, the number of patients prescribed dupilumab by a dermatologist in Sweden in 2021 was retrieved from the pharmaceutical database of The National Board of Health and Welfare (NBHW) and compared with the number of patients on dupilumab in SwedAD. The rate was approximately 40% for the nation, but varied between regions.

DISCUSSION

A valid nationwide quality registry is dependent on relevant outcome measures, high data density and good coverage. To achieve good coverage, the interface must be easy to navigate, and the amount of time required to enter data minimized. The importance of this is underscored when the registry aims for national coverage with many participating clinics. In the establishment of SwedAD the list of outcomes measures and other variables has been carefully considered and edited with this in mind. Much attention has been given to the practical aspects of data input for the convenience of patients and clinicians. The “less is more” approach has been a guiding principle, with a preference for fewer, but well-chosen, outcome measures that are likely to be reported. The interface of SwedAD accepts registration of a patient despite missing data. It is hoped that this has been beneficial for the overall coverage rate of the registry. Meanwhile, the steering group acknowledges that this approach might come at the expense of missing data for some background characteristics. Most of the missing information can be added later. One strategy to reduce administrative work has been that data is reported by the patients themselves on an electronic device and then encrypted and downloaded directly to SwedAD. The process of streamlining data input is on-going.

The steering group opted to omit extensive reporting of comorbidities and concomitant medication except

for basic atopic comorbidities at the time of enrolment. Every person born in Sweden, as well as every person who resides in the country for more than 1 year, is assigned a unique personal identity number. The personal identity number is used in most spheres of society (healthcare, education, retail, banking, etc.) as well as in registries. Thus, there are highly reliable national population registries covering all inhabitants of Sweden and their life events, such as birth, disease, cause and time of death, marital status, family relationships and migration (22). The main purpose for these registries, held by SCB and the NBHW, are to provide complete population-based data to the government and healthcare authorities to facilitate analyses and decisions. Registry data are also an important part of Swedish medical and epidemiological research. After ethical approval and in compliance with the General Data Protection Regulation (GDPR), the personal identity number enables linkage between different registries with high accuracy. In this way, population-based registries with information on morbidity or medication can be linked with SwedAD for scientific purposes. Researchers do not have to rely on patient-reported data, which might be misinterpreted or biased.

At present, it is not mandatory for Swedish dermatology clinics to join SwedAD. Registry participation is not monitored or enforced by healthcare authorities. The steering group recognizes that the voluntary incentive to enrol patients has led to good coverage in participating clinics. Other clinics hesitate to join due to lack of time and resources for the extra effort involved. In less densely populated areas of Sweden, there may be few dermatologists, which is probably reflected in the lower rate of enrolled patients in the northern part of the country.

Sweden is divided into 21 counties, which may have different political governing based on regional elections. This leads to autonomy with regards to certain aspects of healthcare organization. In some regions, patient fees for private dermatology are subsidized from public healthcare funds in order to increase availability of care. This applies to the most populous and third most populous urban areas (Stockholm and Malmö, respectively) in Sweden, where many patients therefore see a private dermatologist. Few private dermatology clinics have so far chosen to join SwedAD. Although inarguably beneficial for the patients, partaking in SwedAD is neither financially nor politically incentivized in these systems, leading to skewed geographical coverage. Since new systemic pharmacotherapy for AD is a large cost for society regardless of who prescribes it, policymakers could argue that follow-up in a quality registry should be mandatory.

The total number of patients with AD receiving systemic pharmacotherapy in Sweden is unknown. Hence, there is no obvious way to determine the national coverage rate of SwedAD. It was assumed that, during

2021, virtually all prescriptions of dupilumab by a dermatologist were intended for AD, even though a very small proportion of these prescriptions were intended for other diagnoses (23–25). The pharmaceutical database of the NBHW logs every dispensed pharmaceutical and the specialty of the prescribing doctor, but not the diagnosis. The number of patients prescribed dupilumab by a dermatologist was retrieved from the database and compared with the number of patients on dupilumab enrolled in SwedAD, reaching a coverage rate of 40% by the end of 2021. Several other systemic pharmacotherapies are registered in SwedAD. Since they are not exclusively prescribed for AD by dermatologists, their prescription statistics could not be used to estimate coverage. The number of enrolled patients in SwedAD has increased by 55%, from 548 at the end of 2021 to 850 in November 2022, which, it is hoped, reflects an increasing coverage rate.

In 3 years, SwedAD has become established as a recognized quality registry with many included patients. This has been accomplished due to a high level of interest from dermatologists and patients and despite the challenges of the COVID-19 pandemic. One of the first real-world studies to report dupilumab-associated conjunctivitis was based on SwedAD registry data (11). Another study based on SwedAD data showed a significant mean weight gain of 6.1 kg among patients after 1 year of treatment with dupilumab (26). The impact of systemic pharmacotherapy for AD on symptoms of depression was recently demonstrated in a prospective clinical cohort study utilizing SwedAD (27). Using the outcome measures recommended by HOME has enabled SwedAD to take part in an international collaboration with registries in the Netherlands, Belgium, Germany, UK, Ireland, France, Spain, Italy, and Denmark as part of the TREAT Registry Taskforce initiative. As of 1 May 2022, SwedAD accounted for 637 of the 4,702 patients enrolled in those registries combined. It was concluded that pooled analyses across all registries are possible for core data items of significance for assessing the effectiveness and safety of AD pharmacotherapy (28).

It is important to increase coverage and data density to further strengthen SwedAD as a nationwide quality registry. Current data imply that access to systemic pharmacotherapy and/or participation in SwedAD is not yet equally available for all patients in Sweden. It is hoped that the registry can highlight and help to combat any such differences by providing relevant data to healthcare authorities. The steering group and the patients' organization are continuously promoting SwedAD among dermatologists and working for improvements in data collection and presentation. Future perspectives include a viewing interface for patients, where they can access their own outcome on a timeline, and a visualization platform for participating clinics, where they can compile and display data regarding their patients.

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The research registry was approved by the Regional Ethical Review Board in Stockholm; 2010/345-31/2. The current study was approved by Ethical Review Board; Dnr 2022-01853-01.

Conflicts of interest. MA has received speaker honoraria and/or been in advisory boards for AbbVie, Eli-Lilly, LEO Pharma, Pfizer, and Sanofi-Genzyme, and is/has been an investigator for AbbVie, and Sanofi-Genzyme. AS has received speaker honoraria from Janssen and been a consultant for AbbVie, Eli Lilly, ICON plc, and Novartis. LHS has received speaker honoraria and/or been in advisory boards for Abbvie, Eli-Lilly, LeoPharma, Pfizer, and Sanofi-Genzyme. LUI has received speaker honoraria and/or been a consultant for AbbVie, ACO, LEO Pharma, Novartis, and Sanofi-Genzyme. AJ has received speaker honoraria and/or been in advisory boards for AbbVie, ACO, Eli-Lilly, and Sanofi-Genzyme. LvK has been a speaker, advisory board member, and/or investigator for Eli Lilly, Leo Pharma, Pfizer, and Sanofi-Genzyme. ML has received speaker honoraria from AbbVie and Sanofi-Genzyme. MHSF has received speaker honoraria and/or been in advisory boards for Almirall, Astellas, AstraZeneca, AbbVie, Celgene, Galderma, LEO Pharma, Lilly, MEDA, Novartis, Sanofi-Genzyme, and Wyeth. GS has received speaker honoraria from AbbVie. ASn has received speaker honoraria and consulting fees from AbbVie, LEO Pharma, Pfizer, and Sanofi. Payments were made to ASn's institution. ASn has been an investigator for AbbVie. SV has received speaker honoraria and been a consultant for Sanofi Genzyme and has received speaker honoraria which were paid to Atopikerna from LEO Pharma and Sanofi-Genzyme. C-FW has participated in expert meetings with AbbVie and Sanofi-Genzyme without receiving personal financial compensation. MB has received speaker honoraria and/or been in advisory boards for AbbVie, ACO, LEO Pharma, Pfizer, Novartis, and Sanofi-Genzyme, and is an investigator for AbbVie. EKJ has received speaker honoraria and/or been a consultant for AbbVie, ACO, Galenica, LEO Pharma, Novartis, and Sanofi-Genzyme.

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