Severe and ChRonic Atopic dermatitis Treatment CoHort (SCRATCH): A Danish Real-world Evidence Atopic Dermatitis Treatment Registry

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Data from real-world use of new systemic treatments in atopic dermatitis (AD) is important for assessing safety and efficacy. The aim of this study is to describe the baseline characteristics of adult patients with moderate-to-severe AD enrolled in the Danish nationwide Severe and ChRonic Atopic dermatitis Treatment CoHort (SCRATCH) database, between October 2017 and August 2021. A total of 282 adult patients were included. Most (62%) were men, the median age at baseline was 43 years (interquartile range (IQR) 29–54 years), and median age at onset of AD was 1 year (IQR 0–6 years). The median Eczema Area and Severity Index at treatment initiation was 19.1 (IQR 11.9–25.7); median Patient Oriented Eczema Measure 21.0 (IQR 16.0–25.0); median Dermatology Life Quality Index 13.0 (IQR 7.0–19.0); and median itch and sleep numerical rating scale scores 8.0 (IQR 6.0–9.0) and 6.0 (IQR 4.0–8.0). Differences were found between the sexes. This registry will provide a source for future efficacy and safety studies.

Key words: atopic dermatitis; baricitinib; dupilumab; real-world; registry; treatment.

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A topic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease, with a lifetime prevalence of up to 20% in children and 2–5% in adults (1). AD usually begins in early childhood, more than half of patients experience persistent or intermittently active disease throughout the remainder of their childhood, and 10–20% have persistence of AD into adulthood (2). Patients with AD have itchy skin that can be triggered by certain stressors, often complicated by skin pain and sleep problems (3). Common comorbidities of AD include rhinitis, asthma, conjunctivitis, and food allergy, but systemic autoinflammatory and infectious diseases can also occur (4–6). In recent years, the association between AD and mental health problems, including suicidal ideation, has been increasingly recognized (7).

The cornerstone of treatment for AD includes patient education, trigger avoidance, and daily use of moisturizers. If needed, this can be supplemented with topical anti-inflammatory agents including topical corticosteroids (TCS) and calcineurin inhibitors (TCI) as reactive or proactive treatment (8). When AD cannot be controlled, the use of systemic immunosuppressants, such as cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil, as well as biologics and small-molecules should be considered (9). In 2018 and 2021, dupilumab and baricitinib were approved for treatment of moderate-to-severe AD in adults in Denmark.

This article describes the organization of the nationwide Danish AD treatment registry “Severe and ChRonic Atopic dermatitis Treatment CoHort” (SCRATCH), including patients with AD who are treated with recently approved systemic treatments indicated for moderate-to-severe AD, as well as demographic and clinical characteristics of patients enrolled into the cohort between October 2017 and August 2021.

MATERIALS AND METHODS

Danish healthcare system

There is free and equal access to the healthcare system in Denmark, with general practitioners (GPs) as gatekeepers (10). Nearly all Danish paediatric and adult patients with AD initially present to their GP for diagnosis and treatment. Patients with more severe
or persistent disease, complications, suspicion of differential diagnoses, or relevant comorbidities, a need for allergy work-up, or other relevant indications, will typically be referred to a private dermatologist, allergist, or, for children, a paediatrician, for further work-up and treatment. If management is not possible in a secondary setting, patients are normally referred to dermatology departments in nearby hospitals for systemic treatment (11). Denmark currently has 6 hospitals with dermatology departments distributed across the country (Fig. S1).

National criteria for treatment of patients with atopic dermatitis with new systemic medications

Treatment with biologics and other new expensive systemic medications for AD is centralized at the dermatology departments, in order to increase experience and restrict the use of such medication. The Danish Dermatological Society has developed guidelines for the treatment of AD, and the Danish Medicines Council has defined criteria for prescription of this medication (8). Since January 2018, dupilumab has been approved for use in adults with moderate-to-severe AD (according to Danish treatment guidelines that is 1 or more of the following Eczema Area and Severity Index (EASI) >16, Body Surface Area (BSA) >10%, Dermatology Life Quality Index (DLQI) >10 or Patient Oriented Eczema Measure (POEM) >16) who have not responded adequately to at least 2 systemic treatments, or have contraindications to them. In April 2020 the indication for dupilumab was expanded to also include adolescents (12–17 years) with treatment failure of 1 systemic therapy, and in June 2021 children aged 6–12 years were also included. At the same time, the JAK-inhibitor, baricitinib was approved for treatment of moderate-to-severe AD and the recommendations for adults were changed, so that failure of only one systemic treatment was required before prescription of either dupilumab or baricitinib was possible. The current recommendation is to clinically assess the treatment effect of dupilumab or baricitinib 16 weeks after initiation of treatment. Treatment should be discontinued if there is no effect on the signs and symptoms of AD. The Danish guidelines suggest that, after 16 weeks of treatment, EASI-75 is considered to be a good response. Patients with EASI-50 and a 4-point decrease in DLQI score are considered partial responders and continue treatment for another 3 months followed by a new assessment.

SCRATCH database

SCRATCH is a nationwide multi-centre registry aiming to include all Danish patients with AD treated with new systemic medications. The database is a tool for clinicians and patients, that allows easy overview of relevant treatment measures and monitoring of effect and safety. Based on the patient’s signed consent, the data in SCRATCH can be used for research purposes. Funding for the creation and operation of the database has, so far, been based on unrestricted research grants from Sanofi-Genzyme, but the intention is to establish agreement with all interested pharmaceutical companies. ZiteLab ApS, a private software developer, (Frederiksberg, Denmark) is providing the encrypted, web-based database used for collecting and storing data. The research project is approved by the Danish Data Protection Agency (P-2019-746).

The SCRATCH database adheres to TREAT registry recommendations (12). At baseline visit, specific information regarding family history of atopy, age at onset of AD, anatomical localization of AD, AD triggers, use of moisturizer, height, weight, comorbidities, educational level, sick-leave due to AD, Work Productivity and Activity Impairment (WPAI), DLQI, POEM, and itch- and sleep scores within the last 3 days (numerical rating scale; NRS 0–10) are collected from the patient. The dermatologist determines the Eczema Area and Severity Index (EASI) score, and records concomitant topical- and systemic treatments. At follow-up visits, adverse events and medication dosage and frequency, together with EASI scores, are recorded. If treatment is paused or stopped, a reason is given by the physician.

Study design and participants

This study evaluated data from a Danish multi-centre prospective cohort of patients with moderate-to-severe AD initiating recently approved systemic treatment in routine clinical care between October 2017 and August 2021. Visits were conducted by dermatologists or residents in dermatology at 6 hospital departments in Denmark. Participation in this study required signed consent from the patient. Children (<18 years) were excluded from the current study, but are also enrolled in the database. Concomitant topical or systemic treatment was permitted, and no wash-out period was required, but participants who went directly from clinical trial of dupilumab into regular treatment with dupilumab were excluded.

Fig. 1. Previous or current systemic and topical atopic dermatitis treatment. TCS: topical corticosteroids. Data on “No earlier systemic treatments” not shown.
Three participants started early-access treatment in October 2017 after special approval from the Danish Medicines Agency, while the rest of the population started treatment after regular approval from the Danish Medicines Council in January 2018.

Statistical analysis

Summary statistics were generated and expressed as frequencies for categorical variables, and medians and interquartile range (IQR) for non-normally distributed variables. Results were stratified according to sex. Cells with fewer than 3 observations are not presented. The software freeware R was used for analysis (version 4.0.5) (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

RESULTS

Informed consent was obtained from 282 patients enrolled in the SCRATCH database. Baseline demographics and patient characteristics are presented in Figs 1–3, Tables I–II, Tables SI–SIV and Fig. S2. All patients were treated with dupilumab. Most participants were males (61.7%), and the median age at enrolment was 43 (IQR 29–54) years (Table I). Women were slightly older than men, being 46 (IQR 29–57) vs 42 (IQR 28–52) years. Median age at AD onset was 1 (IQR 0–6) year, 6 months (IQR 0–6 years) and 2 (IQR 0–6) years for women and men, respectively. Differences were observed between the 2 sexes in educational levels. Thus, 32.4% of women had completed a medium- to long-cycle higher education compared with 17.2% of men. Sixty-three percent had at least 1 first-degree relative with atopy. The most common atopic disposition was having a sibling with rhinitis (22.0%), followed by a parent with AD (20.6%) or rhinitis (20.6%). More than three-quarters had AD on their face/neck region (78.3%), followed by the trunk (74.2%), legs (62.7%), scalp (57.6%), elbow crease (57.1%), hands (53.0%), popliteal (47.0%), feet (37.8%) and crotch (23.5%) (Fig. S2). Alternative treatments had been tried by 27.2% of patients, more women (35.8%) than men (20.9%).

The most frequently reported AD trigger factors (Fig. 2, Table SII) were sweating (75.7%), heat (10%), stress (14%), dust/mite (14%), sleep deprivation (10%), and cat (7%). The most common comorbidities at baseline were urticaria (62%), depression (32%), hypertension (14%), anxiety (14%), migraine (7%), and low temperatures (7%).

Fig. 2. Atopic dermatitis trigger factors at baseline.

Fig. 3. Previous and current comorbidities at baseline. ADHD: attention deficit hyperactivity disorder, ADD: attention deficit disorder.
Patients often reported previous or current rhinitis (79.3%), asthma (70.4%), food allergy (52.4%), and conjunctivitis (51.2%) (Table I). The most prevalent, non-atopic, comorbidities were urticaria (31.6%), depression (14.2%), and hypertension (13.8%) (Fig. 3, Table SIII). Women reported most comorbidities more frequently than men, especially osteoporosis, migraine, anxiety, urticaria, and depression. Before initiating new systemic treatment, most (83.6%) had been treated with 2 or more systemic medications, azathioprine being the most frequent (77.3%), followed by methotrexate (75.5%), prednisolone (54.1%), cyclosporine (30.0%), and mycophenolate mofetil (20.5%) (Fig. 1, Table SI).

Ninety-three percent of patients were treated concomitantly with topical anti-inflammatory agents, most with a potent (67.5%) or moderately potent (44.4%) TCS. All participants used moisturizer at least once a week. Most participants (78.3%) used moisturizer several times a day, 17.0% once a day, 1.9% every second day, and 2.4% 2–3 times a week (Table I).

The median baseline EASI score was 19.1 (IQR 11.9–25.7), POEM 21.0 (IQR 16.0–25.0) and DLQI 13.0 (IQR 7.0–19.0).

### Table I. Baseline characteristics of a study population with moderate-to-severe atopic dermatitis (AD)

|                  | Total | Females | Males |
|------------------|-------|---------|-------|
| **Sex, n; %**    | 282   | 108     | 174   |
| **Age at baseline, years** | 282   | 108     | 174   |
| **Body mass index, kg/m²** | 206   | 85      | 121   |
| **Age at debut, years** | 209   | 86      | 123   |
| **Receiving education, n; %** | 9     | 3.2     | 174   | 2.9 |
| **Primary, n; %**  | 31    | 11.0    | 14     | 9.2  |
| **Secondary, n; %** | 30    | 10.6    | 14     | 9.2  |
| **Vocational education, n; %** | 31    | 11.0    | 4      | 77.3 |
| **Short-cycle higher education, n; %** | 45    | 16.0    | 15     | 30.0 |
| **Medium-cycle higher education, n; %** | 24    | 8.5     | 17     | 7.4  |
| **Long-cycle higher education, n; %** | 41    | 14.5    | 18     | 4.0  |
| **Missing, n; %** | 282   | 108     | 114   |
| **At least 1 first-degree relative with atopy, n; %** | 178   | 75      | 103   | 59.2 |
| **Sibling with AD, n; %** | 49     | 17.4    | 18     | 17.8 |
| **Sibling with asthma, n; %** | 44     | 15.6    | 18     | 17.8 |
| **Sibling with rhinitis, n; %** | 62     | 22.0    | 27     | 20.1 |
| **Parent with AD, n; %** | 58    | 20.6    | 22     | 19.5 |
| **Parent with asthma, n; %** | 47     | 16.7    | 22     | 13.2 |
| **Parent with rhinitis, n; %** | 58     | 20.6    | 22     | 13.2 |
| **Parent, do not know, n; %** | 43     | 15.2    | 18     | 14.4 |
| **Own atopy**     |       |         |       |
| **Rhinitis current, n; %** | 208    | 65.4    | 87     | 62.1 |
| **Rhinitis previously, n; %** | 29     | 13.9    | 15     | 11.6 |
| **Asthma current, n; %** | 213    | 52.6    | 89     | 43.8 |
| **Asthma previously, n; %** | 38     | 17.8    | 20     | 20.2 |
| **Food allergy current, n; %** | 210    | 42.4    | 86     | 43.0 |
| **Food allergy previously, n; %** | 21     | 10.0    | 8      | 9.3  |
| **Conjunctivitis current, n; %** | 211    | 15.2    | 9      | 10.1 |
| **Conjunctivitis previously, n; %** | 76     | 36.0    | 35     | 39.3 |
| **Use of moisturizer** | 212    | 89      | 123    |     |
| **Several times a day, n; %** | 166    | 78.3    | 76     | 85.4 |
| **Once a day, n; %** | 36     | 17.0    | 12     | 13.5 |
| **Every second day, n; %** | 4      | 1.9     | 0      | 0.0  |
| **2–3 times a week, n; %** | 5      | 2.4     | N/A    | N/A  |
| **Once a week, n; %** | N/A    | N/A     | N/A    | N/A  |
| **Never, n; %** | 0      | 0.0     | 0      | 0.0  |

### Table II. Severity of atopic dermatitis and its impact on quality of life at baseline

|                  | Total | Females | Males |
|------------------|-------|---------|-------|
| **Eczema Area and Severity Index (0–72 points)** | 231   | 87      | 144   |
| **Patient Oriented Eczema Measure (0–28 points)** | 223   | 89      | 134   |
| **Dermatology Life Quality Index (0–30 points)** | 210   | 88      | 122   |
| **Itch score (numerical rating scale 0–10)** | 232   | 94      | 138   |
| **Sleeplessness score (NRS 0–10)** | 229   | 92      | 137   |

IQR: interquartile range; N/A: not applicable.

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Prospectively collected real-world data from patients with moderate-to-severe AD provide multiple benefits. As opposed to clinical trials, in which strict inclusion and exclusion criteria exist, real-world AD treatment registries, such as SCRATCH, enrol consecutive patients, with AD being treated with new targeted and selective medications independent of, for example, duration of AD, previous or current comorbidities, and medication use. Garcia-Doval et al. (13) concluded that 30% of their real-world study population with psoriasis would have been ineligible for clinical trials due to age, disease phenotype, or comorbidities. In a real-world setting, patients and physicians may choose to change dosage and treatment intervals as well as combine several medications at the same time, which will shed new light on the relative effect and safety of new medications. Another benefit from real-world registry data is that putative treatment effects on comorbidities can be studied, e.g. allergic asthma, rheumatoid arthritis, and alopecia areata, ultimately improving understanding of the disease (14–16). Factors that may affect the medication efficacy estimates in clinical trials, e.g. the eligibility creep (i.e. the tendency for physicians to score borderline patients higher when assessing eczema in order to meet eligibility criteria), altered patient behaviour (e.g. increased showering and emollient adherence during trials), and regression towards the mean (i.e. very sick patients will have an increased chance of improving compared with patients with milder disease) following wash-out are not a concern in real-world studies (17).

Many European countries collect similar data on patients with moderate-severe AD, including TREATGermany (Germany), A-STAR (UK and Ireland), TREAT-NL (the Netherlands and Belgium), BioDay (the Netherlands), Biobadatop (Spain), FIRST (France), SwedAD (Sweden) and AtopyReg (Italy). The real-world use of dupilumab has recently been examined in various registers; however, only a few studies include study populations > 200 patients (18–21). The demographics of Danish patients initiating dupilumab treatment and registered in SCRATCH are, to date, comparable to those from other European centres: most patients are men (61.7%; 57.7%; 56.4%; 60.0%; 57.5%; and 61.4% in Denmark, Germany, Italy, France, TREAT-NL and BioDay, respectively), and the mean age at inclusion is similar (43, 42, 41, 37, 41, and 43 years in Denmark, Germany, Italy, France, TREAT-NL and BioDay, respectively) (22, 23). The male predominance is in contrast to Danish register studies reporting women to constitute two-thirds of the adult AD population seen in Danish hospitals, suggesting more severe, persistent or treatment-resistant disease in men, as they seem to more frequently qualify for biological therapy (24). Patients mainly have early onset AD, with a median debut age of 1 year and 0 years in the Danish and TREAT-NL populations, respectively. Approximately 2 out of 3 patients had asthma in the Danish (70.4%), French (66.0%), TREAT-NL (64.7%) and BioDay (59.0%) study populations, while the occurrence of patient-reported rhinitis and food allergy was higher in the Danish (79.3% and 52.4%) and BioDay (69.0% and 48.1%) populations than in the French (57.1% and 25.9%) and Italian (46.8% and 15.5%) populations, which is probably explained by the nature of data collection (self-report vs clinician assessed).

AD severity is also comparable between the centres. The Danish patients had an EASI of 19.1, while TREAT-NL, BioDay, French and Italian populations had a median EASI of 21.4; 19.0; 18.3 and 28.0, respectively. The POEM and DLQI scores were also similar (POEM 21.0; 25.9 and 20 in Denmark, TREAT-NL and BioDay, respectively, and DLQI 13.0; 17.0; 14; 19.6 and 12 in Denmark, Italy, France, TREAT-NL and BioDay; respectively). The TREATGermany population was, overall, slightly less affected, with an EASI of 16.1, POEM of 16.8 and DLQI of 11.8, probably due to differences in inclusion criteria (studies by Siegels et al. (22) and Heratizadeh et al. (23) include patients with AD in systemic therapy, not only dupilumab). Women had lower EASI scores, which was also found in the TREAT-NL population, but reported greater effects on sleep and quality of life. Scores were, especially concerning baseline EASI, very different from results from phase 3 trials, which is not surprising, due to their inclusion criteria and wash-out period prior to treatment initiation (25). Involvement of the head and neck was frequent in the Danish (face/neck 78.3%) and the German study population (face 78.0% and neck 78.0%), while the majority (90%) of the Italian study population reported diffuse localization and only 8% described head and neck involvement.
Differences in treatment patterns between countries are elucidated by data on previously used therapies before initiating biological treatment. Danish patients had mostly tried azathioprine (77.3%) and/or methotrexate (75.5%), while most TREAT-NL, BioDay and French patients had been treated with cyclosporine (89.1%; 95.7% and 74.9%, respectively), and most Italian patients had tried oral glucocorticoids (89.5%) prior to dupilumab treatment. Most Danish patients had tried 2 or more systemic therapies, fitting well with national treatment recommendations. Treatment patterns were similar for women and men, except more women had tried methotrexate, which is surprising, due to the teratogenic effect of methotrexate.

Most frequently reported AD triggers were sweat (75.7%), hot weather (73.8%), and stress (73.8%), which is in accordance with previous research, although more prevalent in the current study population (26). The number of trigger factors is related to AD severity, presence of hay fever, and food allergy and lower age at AD onset, which might explain the high occurrence in the current study population. Women generally reported the triggers more frequently than men, especially wool, infections, chlorinated water, and stress. Men reported grass pollen as a trigger more than women. One in 4 had tried alternative medicine, which is somewhat fewer than in another Danish study of patients with moderate AD (43.0%). The findings of the current study emphasize the influence of AD on workability, with patients reporting affection of work productivity and 67.7% of patients ever being on sick leave because of their AD. This is markedly higher than 9.7% reporting sick leave (defined as more than 7 days away from work) due to eczema in a Swedish study and 42% taking sick leave in the past year in a Dutch study, probably explained by study differences in AD severity, definition of sick leave and timing (ever vs past year) (27, 28). Treatment with dupilumab has demonstrated a significant improvement in work productivity after 52 weeks in a study from the BioDay registry (29).

Strengths and limitations

This study was nationwide, but it did not collect information on the proportion of patients that was not included in the databases, e.g. due to physician neglect, or patient refusal. It is our impression that only a small proportion of patients is not included. SCRATCH adheres to TREAT guidelines and, accordingly, uses relevant and verified tools for measuring AD domains. Via linkage to Danish registries, SCRATCH has unique potential and perspectives; for example, it would be possible to follow and study AD activity over time. Since results arise from a daily practice setting, several limitations will apply. Collection of data is based on active participation by both patients and clinicians, and, if data is not or only partly entered into the database, then the quality of the data extracted will decrease correspondingly. Currently, for user ease, some important perspectives on, for example, comorbidity activity, skin dryness and contact sensitization, have not been collected. As data is derived from 6 hospitals in Denmark, many different clinicians participate in providing data, which could potentially cause some interobserver differences. Clinicians and patients are non-blinded, which could impact their answers and ratings.

Conclusion

Real-world evidence is crucial when new medication is marketed to examine safety and efficacy. The study presents the demographics of Danish adults who entered the SCRATCH database between October 2017 and August 2021 and shows that they are comparable to patients from other European centres. In addition, striking differences were observed between men and women.

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