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TITLE PAGE

TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for a European safety study of dupilumab and other systemic therapies in patients with atopic eczema

Short title: TREAT safety study protocol

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What's already known about this topic?

- There is a need for long-term data on the safety of systemic immunomodulating therapies in patients with atopic eczema.
- Regulatory bodies, such as the European Medicines Agency, increasingly stipulate the collection of such data as part of the licensing agreement for new treatments to assess the new agent's long-term safety profile against established therapies.
- Large numbers of patients with a long duration of follow-up are necessary in order to detect rare events like malignancies.

What does this study add?

- The TREAT Registry Taskforce offers a platform to conduct such research with a network of multiple national atopic eczema research registries.
- We present a protocol for an investigator-initiated multicenter safety study comparing dupilumab with other systemic immunomodulating therapies in adults and subsequently adolescents and children with moderate-to-severe atopic eczema.
- This protocol can be used as a framework for similar studies for other novel systemic immunomodulating therapies across both adult and paediatric populations.

ABSTRACT

Summary (abstract)

Background: A long-term prospective observational safety study is essential to fully characterize the safety profile of systemic immunomodulating therapies for patients with atopic eczema. The TREatment of ATopic eczema (TREAT) Registry Taskforce offers a large platform to conduct such research using national registries that collect the same data using a predefined core dataset.

Objectives: We present a protocol for a safety study comparing dupilumab with other systemic immunomodulating therapies in children and adults with moderate-to-severe atopic eczema to assess the long-term safety risk of these therapies in a routine clinical care setting.

Methods: We describe a registry-embedded international observational prospective cohort study. Adult and paediatric patients who start treatment with dupilumab or anothersystemic immunomodulating agent for their atopic eczema will be included. The primary endpoint is

the incidence of malignancies (excluding non-melanoma skin cancer) compared between the treatment groups. Secondary endpoints include other serious adverse events and adverse events of special interest, such as eye disorders and eosinophilia.

Conclusions: This protocol delineates a safety study for dupilumab in adult and paediatric patients with atopic eczema, using a standardized methodological approach across several national registries. The protocol could also be used for other novel systemic immunomodulating therapies and could provide licensing and reimbursement authorities, pharmaceutical companies and clinicians with safety evidence from a routine clinical care setting.

BODY TEXT

Introduction

In a substantial number of patients with atopic eczema systemic immunomodulating therapies are required because the disease is not sufficiently controlled with topical therapies.[1] Ciclosporin was until recently the only systemic treatment approved in Europe and only in adults with severe disease.[2] The frequency and duration of the use of ciclosporin is limited due to the risk of renal toxicity and hypertension. In addition, neurological symptoms, fatigue or gastrointestinal symptoms, next to treatment failure are reasons for patients to discontinue their treatment.[3] Ciclosporin has many potential contra-indications and drug interactions. Alternative systemic immunomodulating therapies are used off-label and include methotrexate, mycophenolic acid, mycophenolate mofetil and azathioprine.[4] These treatments are frequently prescribed for atopic eczema.[5, 6] Methotrexate has limitations due to potential

liver toxicity and teratogenicity.[7] Azathioprine and ciclosporin have been associated with an increased risk of incident cancer.[8-11] However, the relative contribution of the diseases themselves and disease-related risk factors are difficult to separate from treatment-related factors.

Dupilumab, a monoclonal antibody binding to the alpha subunit of the interleukin-4 receptor (IL-4Rα), has recently been approved by both the Food and Drug Administration (FDA) in the U.S.A. and European Medicines Agency (EMA) for the treatment of adult patients with moderate-to-severe atopic eczema. Regarding short-time safety, clinical trials on dupilumab have shown no significant difference in the proportion of patients with at least one adverse event in comparison to placebo, nor were there serious adverse events related to dupilumab. Injection-site reactions and conjunctivitis were the most commonly reported adverse events.[12, 13] Eosinophilia has been reported in trials investigating dupilumab treatment in patients with asthma, with symptomatic hypereosinophilia being observed in rare cases.[14, 15] In atopic eczema studies asymptomatic eosinophilia has been observed.[12, 16] In addition, conflicting evidence exists about the role of IL-4 in tumor promotion.[17, 18] The long-term safety of dupilumab has not yet been investigated.

In order to fully characterize the safety profile of the long-term use of dupilumab and mostly off-label systemic treatments among patients with atopic eczema, a long-term, prospective, observational safety study is essential and often stipulated by the licensing body, such as the EMA. Clinical registries can provide such data.

The TREatment of ATopic eczema (TREAT) Registry Taskforce is an international network of research registries which collect observational data of adult and paediatric patients with atopic eczema in a harmonized fashion.[19] Consensus was reached on a core dataset based on an international Delphi exercise among over 400 stakeholders from over 20 countries.[20, 21] Recently, recommendations for measurement instruments have been added to this core dataset.[22] Currently, TREAT registries are being established in different European countries and in North America. Countries participating in the TREAT registry initiative are the U.K., Ireland, the U.S.A., Germany, the Netherlands, Denmark, Sweden, France, Italy, Spain and Portugal.

Data collected in a harmonized and standardized fashion across the TREAT registries can be used for the purpose of conducting a long-term safety study and here we present a study protocol for such an approach. The main objective of this study is to characterize the long-term safety profile of dupilumab compared to other systemic immunomodulating therapies for the treatment of atopic eczema in a routine clinical care setting.

Patients and methods

Study design

A registry-embedded long-term international prospective cohort study is conducted, aiming to recruit adult and paediatric patients with atopic eczema who start treatment with dupilumab and to compare the adverse event rates in this cohort with a cohort starting treatment with other systemic immunomodulating therapy (e.g. ciclosporin, methotrexate, mycophenolic acid, mycophenolate mofetil and/or azathioprine). The study has an

observational nature where interventions are initiated by the treating physician and not determined by the study. Coordinating centres of this study are the sites that coordinate the atopic eczema registries of the TREAT Registry Taskforce, each with a network of recruiting sites. Our European initiative has been registered as a research network with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).[23]

Patient population

The study population consists of patients with a physician diagnosis of atopic eczema, who are starting on or switching to a systemic immunomodulating treatment for their atopic eczema that they have not received before. We aim to include as many dupilumab-treated patients as those treated with other systemic immunomodulating therapies as contemporaneous comparator. Participants need to be willing to comply with all study requirements and provide consent to participate in long-term follow-up for the collection of observational data during their visits, including adverse event recording and disease severity assessments. Written informed consent is obtained from each patient before participation.

Patients will not be allowed to be enrolled in the study if they are concurrently participating in an interventional study of systemic therapy for atopic eczema. The study participants can be enrolled in clinical trials prospectively. We will record if participants are participating in an investigational trial and include this as a variable in our analysis. If possible, follow-up visits for this safety study will be continued during the investigational trial. Participants can also be co-enrolled in other observational studies.

Study schedule

During the observation period, participants will be assessed on at least a 6 monthly basis while on therapy and at least annually off systemic immunomodulating treatment to collect data on adverse events and reasons for potential changes in therapy. A +/-2 months visit window will be applied. The study aims to monitor patients for as long as possible, aiming for at least 5 years of follow-up for each participant.

Study endpoints

Primary endpoint:

- Incidence rate ratios of cancer (any pathology-confirmed malignant tumour or cancer excluding non-melanoma skin cancer (NMSC)) within the follow-up period comparing the group receiving dupilumab and the group receiving other systemic immunomodulating treatments.

Secondary endpoints:

- Incidence rate ratios of serious adverse events (any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, including serious infections (e.g pneumonia, septicaemia, bone, joint and opportunistic infections)[24]) within the follow-up period comparing the groups.
- Incidence rate ratios of other adverse events of special interest in the groups: eosinophilia (an absolute eosinophil count of ≥500/µl), eye disorders (e.g.

conjunctivitis,blepharitis, and other eye disorders as diagnosed by an ophthalmologist if appropriate), skin cancer (including both melanoma and NMSC), cardiac disorders (e.g. myocardial infarction), central nervous system disorders (e.g. demyelination, peripheral neuropathy, seizures), and haematological disorders (e.g. aplastic anaemia, pancytopaenia).

- Discontinuation rate of dupilumab due to adverse events, compared to the discontinuation of the other systemic treatments.

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Sample size

The definite power calculation will be based on the anticipated frequency of the outcomes. Under the assumption of 80% power and 5% alpha error (2-sided), a hazard ratio (HR) of 2 and 1:1 ratio of patients exposed vs. non-exposed to dupilumab (primary exposure) requires 66 events in the study.[25] Due to non-random allocation of patients between the groups a R2 (r-squared) of exposure to dupilumab explained by other covariates = 0.2 is considered. Assuming an annual incidence rate of any cancer (excluding NMSC) of 33 per 10,000 patients,[26] this results in 82 events.[27] There would be less power to detect the rare cancer specific subtypes, such as lymphoma and melanoma, unless the risk difference is very large. Our assumed HR for this power calculation is in line with the standard EMA requirements for a post-marketing safety study focused on cancer. A safety study should be large enough to detect a two folded increases risk for cancer (without NMSC). If the risk is higher than a HR of 2 the desired 82 cancer events would happen earlier in time and if the risk is smaller than a HR of 2 a larger sample size would be required.

Furthermore, a dropout rate of 20% including those with only limited exposition to dupilumab (exposure to dupilumab < 4 weeks) or other possible future biologicals is assumed. To achieve these 82 events, we are dependent on the number of recruited patients, the speed of recruiting and the time the patients are under observation in the registry. Table 1 gives an overview about possible scenarios if recruitment is uniformly distributed over the recruitment period. By recruiting 1000 patients (N_y) per year over three years (Y_rec) the desired number of 82 events will appear in the 9th year of the study. By recruiting 800 patients per year over four years the desired number of 82 events will also appear in the 9th year of the study but require overall 3200 instead of 3000 patients to be included in the study.

Exposure to dupilumab and other systemic immunomodulating treatments for atopic eczema will vary over time. It is expected that many patients will be exposed to more than one systemic immunomodulating agent within the study period. Differences in previous exposure to systemic immunomodulating atopic eczema treatments also have to be considered as potential confounders in the analysis. Additionally, a certain lag time has to be assumed between relevant exposures and detection of incident cancer. Long latency adverse events, like cancer, will be linked to a drug if patients were ever exposed to the drug. Short latency adverse events, like eye disorders, will be linked to a drug if they took place while the patient was using the drug or within 90 days after the end of exposure.

Statistical analysis

The data from each participating registry will be analysed separately at first. A descriptive analysis of baseline patient characteristics and medical history will be presented. Categorical variables will be summarized by number and percentage in each category. Missing data will be displayed as a separate category where appropriate. Both cumulative incidence and

incidence rates of malignancies, including 95% two-sided confidence intervals, will be estimated for the treatment groups.

The data from each registry will then be pooled and a comparative analysis will be performed on the pooled data to estimate if there is a difference in the incidence rates for malignancies or serious infections and the other adverse events of interest between the treatment groups. In the primary confirmatory analysis exposure to dupilumab will be handled as a binary variable, i.e. patients are classified as exposed if they received dupilumab at least once within the study period; otherwise as non-exposed. The log-rank test will be used followed by cox proportional hazard models. Potential confounders and effect modifiers (age, sex, previous treatments (including previous phototherapy), malignancy history, smoking, family history, co-treatments, socioeconomic position, country etc.) will be tested and included in the cox model if they improve the model fit according to the Bayesian information criterion. Primary population for analysis will be all patients up to the point when 82 cancer events appear. The analyses will take into account switching from one drug to another as well as medical (therapeutic) history, such that the person-years of follow-up switch to the new drug when this is initiated.

Sensitivity analyses will:

- Consider history of malignancy
- Include analyses stratified by cancer type (including NMSC)
- Consider lag time of exposure and cancer incidence of 12 months
- Explore a potential dose-response effect of cumulative dupilumab exposure

The same methods as described above will be applied to analyse secondary outcomes.

Data collection

Each country will use a purpose-built online data entry platform to prospectively collect the study data. All data will be pooled across countries for the final analyses. The pseudonymised data of each national registry will be hosted on secure servers. All data will be additionally stored on a backup server in case of data loss. Only registered local investigators and delegated study members will have access to the data entry platform and only to the data of their own patients.

Data capture includes a case record form (CRF) based on the TREAT core dataset.[21, 22] A variety of parameters will be collected during the study visits. Concerning safety, data on the predefined adverse events, including severity, seriousness, and relatedness to therapy as part of pharmacovigilance will be recorded at each follow-up visit and entered into the CRF. All predefined malignancy and other pre-defined adverse event categories will be recorded using MedDRA (Medical Dictionary for Regulatory Activities) data dictionary coding. Where possible, the use of data from national cancer registries will be explored. In case of loss to follow-up, every effort will be made to collect information on the reason for this, including data on a potential (serious) adverse event related to this.

Study governance structure

The safety study will be governed by a Steering Committee (SC), consisting of the Chair (Study Lead Investigator), the Co-Chair (Deputy Lead Investigator) and all country Principal Investigators (PI) and Co-PIs. The SC will be responsible for the running and management of the study and will meet regularly, at least six monthly, either in person or via teleconference.

In addition, there will be a Data Monitoring Committee (DMC), an independently formed committee with responsibility for monitoring the patient safety. The DMC safeguards the interests of the patients participating in the study. It is the job of the DMC to monitor the comparative data and make recommendations to the SC on whether there are any ethical or safety reasons why the study should not be continued. They can also advise on modifications to the protocol. Apart from its Chair, the DMC will have at least one statistician and at least two clinicians not directly involved in the study, with an interest in pharmacovigilance.

Discussion

The current evidence to inform clinical management for moderate-to-severe atopic eczema stems from a small body of randomized controlled trials.[28-33] The psoriasis literature indicates that approximately 30% of patients entered into registries would be ineligible for clinical trials.[34] In addition, procedures differ between trials and routine clinical practice which impairs the generalizability of the findings. There is no long-term, comparative and observational data on effectiveness and safety of systemic immunomodulating therapies for atopic eczema from a large-scale multicenter international cohort study. Several guidelines and a systematic review highlight these gaps.[35-37]

The overall aim of the described study is to provide data on the long-term safety of dupilumab compared with other systemic immunomodulating therapies for the treatment of atopic eczema in adults and children. The observational nature of the study, using the platform of registries of the TREAT Registry Taskforce, guarantees the collection of data from patients in a routine clinical care setting. The described standardized methodological approach across registries will allow data pooling, in order to obtain the large number of patients required to acquire the power to detect rare events like malignancies.

A limitation of the study is that although the severity of disease requiring dupilumab treatment or another novel systemic agent is likely to be closely comparable to that of those exposed to another systemic immunomodulating drug intervention , the decision to start dupilumab treatment will most frequently be based on access to these novel systemic agents and a lack of suitability of or responsiveness to other immunomodulating therapies rather than on disease severity. This is likely to result in differences between treatment groups, for example in the responsiveness to standard agents, which cannot be quantified other than by fully documenting previous systemic treatments for atopic eczema and then adjust for such confounders in statistical analysis.

Individuals commencing novel systemic treatments have often received multiple systemic therapies in the past. Limiting the study only to new users of such therapies would restrict the dupilumab group to patients with contraindications for many other therapies. This approach would undermine the scope of evidence from the routine clinical care setting and introduce bias.[38] Our data will take into account sequential treatment switching decisions that typically take place in routine clinical practice and that are almost impossible to study in clinical trials.

The need for long-term safety studies for other therapies will increase, as many other novel therapies are currently being assessed in clinical trials. The described study protocol primarily concerns a comparison between dupilumab and other systemic therapies. However, this protocol can be used as a framework for similar studies for other novel systemic immunomodulating therapies across both adult and paediatric populations within the TREAT Registry Taskforce. The described study could be adapted to include and collect on any drug and adverse event of interest. While the presented protocol is focused on dupilumab, we will

also collect similar adverse event data on all other systemic therapies the participants are on. This will allow safety comparisons between all other systemic immunomodulating therapies, provided that the number of treated patients and power is adequate.

This study will run as an investigator-led project but is open to receive financial support from charities, governments as well as pharmaceutical companies, who might want to task the study team with the follow-up of patients on their agents. This approach could provide pharmaceutical companies post-authorization safety data on their systemic therapies as requested by licensing and regulatory bodies.

Next to the countries that have already started, several other countries have shown their interest in joining in the TREAT Registry Taskforce (treat-registry-taskforce.org) and establishing a TREAT registry. This offers opportunities for expansion of this and similar studies for other systemic therapies in the future.

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Supporting information

Not applicable

TABLES AND FIGURES

Table 1: Distribution of follow-up time in years for different recruitment scenarios to achieve estimated event numbers at the end of the year, assuming recruitment is uniformly distributed over the recruitment period with 20% dropout and a background incidence of 33 per 10.000 person years.

N_y	Y_rec	3y	4y	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y
600	3	11	18	25	32	39	45	52	59	66	73	79	86
800	3	14	24	33	42	51	61	70	79	88	97	106	115
1000	3	18	29	41	53	64	76	87	99	110	121	132	143
600	4	11	19	28	38	47	56	65	74	83	92	101	110
800	4	14	25	38	50	62	75	87	99	111	123	135	147
1000	4	18	31	47	63	78	93	109	124	139	154	169	184
600	5	11	19	29	41	53	64	76	87	99	110	121	132
800	5	14	25	39	55	70	86	101	116	131	147	162	176
1000	5	18	31	49	69	88	107	126	145	164	183	202	221

N_y: number of recruited patients per year; Y_rec: duration of recruitment.

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