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ORIGINAL ARTICLE

Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis: Results from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry

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Abstract

Background: Evidence on the (long-term) safety of systemic immunomodulating therapies in atopic dermatitis (AD) generated by real-world data is sparse.

Objectives: To describe real-world reported adverse drug reactions (AEs) related to systemic immunomodulating therapy in patients with AD and to compare the incidence rates of AEs with the Summaries of Product Characteristics (SmPCs).

Methods: We conducted an observational prospective multi-centre cohort study, using the TREAT NL registry. All severe AEs, AEs of special interest and serious AEs in adult and paediatric patients on systemic immunomodulating treatment (ciclosporin, methotrexate, azathioprine, mycophenolic acid, dupilumab, tralokinumab, baricitinib and upadacitinib) were assessed. Incidences rates of all (potentially) drug-related AEs were standardized in patient years and compared to the cumulative incidences in the associated SmPCs.

Results: We collected 422 patient years of safety data from 266 patients, of whom 129 (48.5%) reported a total of 224 (potentially) drug-related AEs. Compared to dupilumab's SmPC, higher incidence rates were found for four AEs (reported ≥5 times): eosinophilia, blepharitis, dry eyes and head and neck erythema (i.e. dupilumab facial redness). A higher incidence rate of fatigue was found in patients on oral methotrexate in our cohort compared to the SmPC. Two new drug-related AEs (reported ≥5 times) were found in patients on dupilumab, including non-infectious conjunctivitis and meibomian gland dysfunction.

Conclusions: Real-world reported AEs captured in AD patient registries can add information on the estimated incidence of AEs and benefit clinical decision aids. Future studies using data derived from the TREAT NL registry combined with data from other registries within the TREAT Registry Taskforce will provide more information on (rare) AEs associated with immunomodulating therapy in AD patients.

INTRODUCTION

Evidence on the (long-term) safety of systemic immunomodulating therapies in atopic dermatitis (AD) generated by real-world data (RWD) is sparse.[1,2] Patients and physicians require clear information on the safety profile of these drugs to assess the risk-to-benefit ratio for shared decision making.[2,3] Decision aids to guide patients and physicians

on the use of specific treatments are often based on the associated Summary of Product Characteristics (SmPC). However, SmPCs might differ from RWD, as the content is mostly based on spontaneous reports, (pre)clinical trials and post-authorization marketing studies.[4]

Most evidence on drug-related AEs is generated by a limited number of randomized controlled trials (RCTs), while a considerable group of AD patients that require systemic therapy is not eligible for clinical trials.[2,5] Moreover, clinical trials often do not include children.[6] On top of this, regulatory agencies rely on post-marketing studies to detect rare AEs, though these studies generally have sample sizes that are too small to improve drug safety surveillance.[7] Consequently, to adequately inform physicians and patients on the safety profile of systemic immunomodulating drugs, discrepancies between RWD and the SmPCs need to be identified. Two recent studies using RWD illustrated new AEs and higher incidences of several AEs compared to the SmPCs in patients with inflammatory bowel disease and rheumatoid arthritis.[8,9] Lastly, numerous systemic therapeutic modalities employed in managing moderate-to-severe AD are prescribed off-label.[10] Consequently, the safety profile of these drugs remains unestablished in the AD population.

Generation of reliable RWD on drug safety and (rare) AEs is one of the main aims of the TREatment of ATopic eczema (TREAT) Registry Taskforce. By means of harmonized data collection in an international network of independent national multi-centre registries, the TREAT Registry Taskforce seeks to better understand effectiveness, safety and cost-effectiveness of systemic immunomodulating therapies for AD.[11–14]

The current study aims to assess the incidence rates of AEs in AD patients treated with systemic immunomodulating therapy and to compare these with the corresponding SmPCs, using RWD from the TREAT NL (the Netherlands and Belgium) registry. Hereby, we strive to increase the knowledge on the safety of these drugs in the moderate-to-severe AD population.

METHODS

Study design and patient population

In this registry-based observational prospective cohort study, data was collected between October 2017 and May 2022 in the following TREAT NL centres (the Netherlands and Belgium): Amsterdam University Medical Centres, Huid Medisch Centrum, Leiden University Medical Centre and University Hospital Ghent. We included all adult and paediatric (<18 years) patients with a physician diagnosis of AD based on the U.K. Working Party criteria, who were starting systemic immunomodulating treatment (ciclosporin, methotrexate, azathioprine, mycophenolic acid, dupilumab, tralokinumab, baricitinib or upadacitinib) for their AD.[15] Visits were conducted by trained healthcare professionals and data was collected using the TREAT core dataset consisting of both patient- and physician-reported domains.[11,12] Patients completed visits at baseline, 4 weeks, 12 weeks, followed by every 12 weeks.

Reporting of adverse events

Severe AEs, AEs of special interest (AESIs) and serious AEs (SAEs) were reported during visits. The definition of these terms can be found in Table 1. Overlap may exist between these groups: for example, a severe AE may also be an AESI. Drug-relatedness of all reported AEs was assessed by the physician and categorized as: not related, doubtful, possible, probable, very likely or definite. The assessment of causality of AEs was based on physician expertise, existing literature or previous reports and the time of occurrence of the AE. If the drug-relatedness of an AE was missing, it was evaluated independently for each AE by two physicians (PS and AM). Moreover, start and stop date of each AE was reported. If the start date of an AE was missing or unknown, the date of visit in which

TABLE 1 Definition of severe adverse events, serious adverse events and severe adverse events of special interest collected in the TREAT NL registry.

Severe adverse events
Any undesirable experience resulting in referral to another specialist, prescription of medication (excl. antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or causing considerable interference with usual activities, whether or not considered related to this treatment.
Serious adverse events (SAEs)[a]
Any experience that results in death; is life-threatening; requires in-patient hospitalization (or prolongation); results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is a serious infection or needed medical intervention to prevent the above from occurring.
Adverse events of special interest (AESIs)
Acne
Arthralgia
Blood and lymphatic system disorders (including eosinophilia)
Cardiovascular disorders
Central nervous system disorders
Dupilumab-induced head and neck erythema
Embolic and thrombotic events
Eye disorders
Gastrointestinal disorders
Hypersensitivity reactions
Lipid disorders
Liver function disorders
Malignancies (including skin cancer)
Serious chronic or relapsing infections (including herpes infections)

[a]Definition according to the Council for International Organizations of Medical Sciences guidelines.[59]

the AE was reported was used as the start date. Also, the action that was undertaken upon the AE (e.g. discontinuation of therapy) and course of the AE were monitored. Persistent AEs were considered solitary events while the second occurrence of an AE was reported as a new event. We collected data on previous or concomitant treatment to identify if an AE was possibly associated with another treatment. For dupilumab, the presence of pre-existent ocular disorders and eosinophilia (>500 cells/mm^3) was assessed. Eosinophilia was only reported as a drug-related AE if it was not pre-existent before treatment initiation. All included patients had eosinophil count measurements at baseline. Information on the presence of pre-existing eye disorders diagnosed by an ophthalmologist was obtained from the medical history. Patients were not routinely evaluated by an ophthalmologist at baseline. When patients complained of eye problems during study visits, they were promptly referred to an ophthalmologist. Diagnosed ocular disorders were then documented and reported as AEs.

All AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) codes, version 25.[16] In this study, Preferred Terms were used to distinct AEs. Subsequently, Preferred Terms were bundled into an organ class, for example, the Preferred Term 'blepharitis' belongs to the organ class 'eye disorders'.[16,17]

Data analysis

Patient characteristics, treatment aspects and an overview of AEs related to each drug were summarized using descriptive statistics. Normality was tested using Shapiro–Wilk tests and Q–Q plots.

Because of differences in size and duration of the different treatment groups, we standardized incidence rates of AEs in patient years. This enabled us to directly compare incidence rates between the different treatment groups. Treatment duration was defined as the time between start and stop date (or last visit date). Patient years are the sum of treatment durations for all patients in years. Incidence rates of each AE are expressed in number of events per patient year. We chose to compare the incidence rates of AEs in our study with the cumulative incidence of AEs in the associated SmPCs, as this is a standardized measure that is independent of the study duration and size, and provides transparency. We assume that the expected risk of AEs remains constant over time. Statistical analyses were performed using SPSS (version 28).[18]

Data presentation

The incidence rates of all AEs that were possibly, probably, very likely and definitely drug-related were compared with the cumulative incidences in the most recent versions of the corresponding SmPCs which were derived from the online database of the Dutch Medicine Evaluation Board.[19–29] Every SmPC contains a section (4.8) 'undesirable effects' where the known AEs and corresponding cumulative incidences are described per organ class, ranging from 'very common' (≥10%) to 'very rare' (≤0.01%).[4] AEs that were doubtfully or not drug-related were not compared to the SmPCs. AEs (reported ≥5 times) with higher incidences compared to the SmPC and new drug-related AEs (reported ≥5 times) were demonstrated in a separate table.

RESULTS

Patient characteristics

A total of 266 patients (55.6% male, median age 33 years, 10.5% paediatric) were included. Baseline characteristics are summarized in Table 2. At the time of enrolment, the majority of patients initiated dupilumab treatment (60.9%), followed by methotrexate (14.2%) and ciclosporin (13.9%).

Severe adverse events, adverse events of special interest and serious adverse events

In total, we collected 422 patient years of safety data. Follow-up time ranged from 0.2 (azathioprine) to 335.5 (dupilumab) patient years. 170 (57.0%) patients reported ≥1 AE(s) (severe AEs, AESIs or SAEs). Of those, 129 patients (59.7% male, median age 40 years, 3.9% paediatric) reported a total of 224 AEs that were categorized as possibly, probably, very likely or definitely drug-related (Table 3). A high treatment discontinuation rate (63.2%) due to AEs was found in patients with AEs related to oral methotrexate. Dosage change due to AEs was more often initiated in patients with AEs related to ciclosporin (18.8%) and oral methotrexate (15.8%) compared to dupilumab (9.7%). Overall, most AEs (58.9%) were still ongoing at the time of the last study visit. None of the AEs were fatal or left residual symptoms.

A total of 177 AESIs were reported, of which 151 were possibly, probably, very likely or definitely drug-related and 26 were doubtful or not drug-related. The vast majority of AESIs included eye disorders ([potentially] related to dupilumab [$n=75$]) and blood and lymphatic system disorders (eosinophilia; [potentially] related to dupilumab [$n=40$], ciclosporin [$n=1$] and oral or subcutaneous methotrexate [$n=4$]). Malignancies (breast cancer [$n=1$], cutaneous T-cell lymphoma [$n=1$], oesophageal adenocarcinoma [$n=1$], transitional cell carcinoma [$n=3$]) were reported in four patients on dupilumab and were categorized as doubtfully or not drug-related.

In total, 41 (11.0%) AEs were categorized as SAEs, of which 2 were possibly or probably drug-related. These drug-related SAEs included a Campylobacter infection leading to hospitalization in a patient on subcutaneous methotrexate, and a toxic reaction (drug hypersensitivity) leading to discontinuation of treatment in a patient on oral methotrexate. However, this toxic reaction may have occurred due to concomitant use of allopurinol.

TABLE 2 Baseline patient characteristics.

	TREAT NL cohort ($n = 266$), n (%) or median (IQR)
Gender	
Male	148 (55.6)
Female	118 (44.4)
Age at enrolment, y	33 (22.8–49.3)
Adult patients (≥18 y)	238 (89.5)
Paediatric patients (<18 y)	28 (10.5)
Body mass index (kg/m^2)[a]	24.2 (22.8–27.1)
Fitzpatrick skin type[c]	
I	15 (5.6)
II	141 (53.0)
III	50 (18.8)
IV	19 (7.1)
V	27 (10.2)
VI	13 (4.9)
Ethnicity[b]	
White	192 (72.2)
Asian	26 (9.8)
Black	22 (8.3)
Other	16 (6.0)
Centre of enrolment	
Amsterdam University Medical Centres	216 (81.2)
Huid Medisch Centrum	21 (7.9)
Leiden University Medical Centre	7 (2.6)
University Hospital Ghent	22 (8.3)
Previously used systemic therapies for AD	
Ciclosporin	167 (33.1)
Systemic corticosteroids	156 (30.9)
Methotrexate	92 (18.2)
Azathioprine	19 (3.8)
Mycophenolic acid	33 (6.5)
Dupilumab	7 (1.4)
Omalizumab	2 (0.4)
Investigational medication	21 (4.2)
Other	8 (1.6)
Systemic therapy started at baseline or restart/switch visit	
Ciclosporin	47 (13.9)
Systemic corticosteroids	2 (0.6)
Methotrexate	48 (14.2)
Azathioprine	1 (0.3)
Mycophenolic acid	4 (1.2)
Dupilumab	206 (60.9)
Tralokinumab	7 (2.1)
Baricitinib	10 (3.0)
Upadacitinib	13 (3.8)

[a]12 missing.
[b]1 missing.
[c]10 missing.
[d]3 missing.

Comparison with the SmPC

Table 4 provides an overview of AEs reported ≥5 times in the TREAT NL registry with a higher incidence rate compared to the associated SmPC. This table also includes new AEs (reported ≥5 times) that are not mentioned in the SmPCs. Compared to the SmPC of dupilumab, higher incidence rates were found in the TREAT NL cohort for eosinophilia (11.9% vs. ≥1%–<10%), blepharitis (3.0% vs. ≥0.1%–<1%), dry eyes (3.6% vs. ≥0.1%–<1%) and head and neck erythema (i.e. 'dupilumab facial redness') (1.5% vs. ≥0.1%–<1%). Of the patients with eosinophilia, hypereosinophilia (≥1500/mm^3) occurred in 17 patients during dupilumab treatment (1500–4050 eosinophils/mm^3), giving an incidence rate of 5.1%. In addition, we found a higher incidence rate of fatigue in patients on oral methotrexate in the TREAT NL cohort compared to the associated SmPC (13.5% vs. ≥1%–<10%).

New drug-related AEs (reported ≥5 times) that were not mentioned in the associated SmPC were found in patients receiving dupilumab and included non-infectious conjunctivitis and meibomian gland dysfunction, with incidence rates of 6.0% and 1.5%, respectively.

A complete overview of AEs related to the various treatments and comparison with the SmPCs are shown in Table 5.

Dupilumab-related ocular AEs

The reported AEs in the organ class 'eye disorders' related to dupilumab use are summarized in Table 6. These AEs are highlighted due to incidence rates and discrepancy to the corresponding SmPC. In total, 80 ocular AEs related to dupilumab treatment were reported in 30 unique patients (76.7% male). Pre-existent ocular complaints (assessed by a physician) before dupilumab treatment were present in 6 patients, who later reported 5 cases of non-infectious conjunctivitis and two cases of conjunctivitis (infectious; bacterial or viral) under dupilumab treatment. In 5 patients (6.3%) dupilumab treatment was discontinued because of ocular complaints, while in 12 cases (15.0%) the dose was adjusted.

Non-infectious conjunctivitis, dry eyes and blepharitis were most frequently reported, with incidence rates of 6.0%, 3.6% and 3.0%, respectively. Corresponding to the SmPC, allergic conjunctivitis and conjunctivitis were commonly observed in the TREAT NL registry, with incidence rates of 2.6% and 1.5%, respectively. In total, non-infectious, infectious and allergic conjunctivitis associated with dupilumab treatment was reported 34 times, giving an incidence rate of 10.1%.

DISCUSSION

In this registry-based observational prospective cohort study, we found five drug-related AEs with higher incidence rates compared to the corresponding SmPCs. These AEs

TABLE 3 Overview of possibly, probably, very likely or definitely drug-related AEs, age and sex distribution among patients with AEs, action upon on AEs, course of AEs, time between start of treatment and occurrence of AEs and follow-up duration, per treatment.

	CsA	MTX, oral	MTX, sc	MMF	Dupi	Tralo	Bari	Upa
Follow-up, patient years	32.6	37.1	4.7	3.2	335.5	1.9	3.9	3.1
Number of patients	47	44	4	4	206	7	10	13
Patients with AEs, *n*	13	14	4	1	91	1	1	4
Male patients, *n* (%)	7 (53.8)	8 (57.1)	2 (50.0)	1 (100)	56 (61.5)	0 (0.0)	1 (100)	2 (50.0)
Female patients, *n* (%)	6 (46.2)	6 (42.9)	2 (50.0)	0 (0.0)	35 (38.5)	1 (100)	0 (0.0)	2 (50.0)
Age at the time of first AE, years, median (IQR)	25.0 (31.0)	27.0 (44.0)	31.0 (34.0)	61	43.3 (27.6)	61	32	25.5 (30.0)
Adult patients, *n* (%)	13 (100)	14 (100)	4 (100)	1 (100)	86 (94.5)	1 (100)	1 (100)	4 (100)
Paediatric patients, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)
Total reported AEs, n	16	36	8	1	154	3	1	5
Very likely or definitely drug-related, *n* (%)	5 (31.3)	2 (5.3)	0 (0.0)	0 (0.0)	8 (5.2)	0 (0.0)	0 (0.0)	3 (60.0)
Possible or probably drug-related, *n* (%)	11 (68.8)	36 (94.7)	8 (100)	1 (100)	146 (94.8)	3 (100)	1 (100)	2 (40.0)
Severe AEs, *n* (%)	11 (68.8)	29 (80.5)	5 (62.5)	1 (100)	23 (14.9)	1 (33.3)	0 (0.0)	1 (20.0)
AEs of special interest, *n* (%)	5 (31.2)	6 (16.7)	2 (25.0)	0 (0.0)	131 (85.1)	2 (66.7)	1 (100)	4 (80.0)
Serious AEs, *n* (%)	0 (0.0)	1 (2.8)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Action upon on AE[a], *n* (%)								
Treatment discontinuation	1 (6.3)	24 (63.2)	0 (0.0)	1 (100)	15 (9.7)	0 (0.0)	0 (0.0)	2 (40.0)
Change in dosage	3 (18.8)	6 (15.8)	0 (0.0)	0 (0.0)	15 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
None	10 (62.5)	2 (5.3)	6 (75.0)	0 (0.0)	115 (74.7)	3 (100)	0 (0.0)	3 (60.0)
Course of AE[b], *n* (%)								
Recovered/resolved	5 (31.3)	8 (21.1)	1 (12.5)	0 (0.0)	21 (13.6)	0 (0.0)	0 (0.0)	1 (20)
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Recovering/resolving	1 (6.3)	1 (2.6)	0 (0.0)	0 (0.0)	13 (8.4)	0 (0.0)	0 (0.0)	2 (40.0)
Not recovered/resolved	5 (31.3)	15 (39.5)	5 (62.5)	0 (0.0)	102 (66.2)	3 (100)	0 (0.0)	2 (40.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	4 (2.6)	0 (0.0)	1 (100)	0 (0.0)
Time-to-onset of first AE[c], weeks, median (IQR)	4.0 (10)	10.0 (49)	7.5 (83)	8.0	12.0 (20)	2.0	7.0	7.5 (9)

Abbreviations: bari, baricitinib; CsA, ciclosporin; dupi, dupilumab; MMF, mycophenolate mofetil; MTX, methotrexate; tralo, tralokinumab; upa, upadacitinib.

[a]2 missing for ciclosporin, 4 missing for oral methotrexate, 2 missing for subcutaneous methotrexate, 9 missing for dupilumab, 1 missing for baricitinib.

[b]5 missing for ciclosporin, 12 missing for oral methotrexate, 2 missing for subcutaneous methotrexate, 14 missing for dupilumab.

[c]1 missing for ciclosporin, 1 missing for oral methotrexate, 3 missing for dupilumab.

TABLE 4 Drug-related AEs (reported ≥5 times) and a higher incidence rate compared to the associated SmPC.

Treatment	Adverse drug reaction	Corresponding organ class	Number of cases	TREAT NL incidence rate (per patient year)	SmPC incidence
Dupilumab	Eosinophilia[a]	Blood and the lymphatic system disorders	40	11.9%	≥1% to <10%
Dupilumab	Blepharitis[b]	Eye disorders	10	3.0%	≥0.1% to <1%
Dupilumab	Dry eyes	Eye disorders	12	3.6%	≥0.1% to <1%
Dupilumab	Meibomian gland dysfunction[c]	Eye disorders	5	1.5%	*Not in SmPC*
Dupilumab	Non-infectious conjunctivitis[d]	Eye disorders	20	6.0%	*Not in SmPC*
Dupilumab	(Head and neck) erythema	Skin and subcutaneous tissue disorders	5	1.5%	≥0.1% to <1%
Methotrexate (oral)	Fatigue	General disorders and administration site conditions	5	13.5%	≥1% to <10%

[a]Eosinophilia is defined by an eosinophil count of >500 cells/mm^3.
[b]Blepharitis is defined as inflammation of the eyelid margins.
[c]Meibomian gland dysfunction is defined as a condition with structural and functional abnormalities of the meibomian glands, often resulting in altered tear film composition and stability.
[d]Conjunctivitis is characterized by conjunctival mucosal inflammation and can be classified as non-infectious (allergic, toxic or non-specific) or infectious (bacterial or viral infections).

included eosinophilia, blepharitis, dry eyes and head and neck erythema related to dupilumab, and fatigue related to oral methotrexate. In addition, we found 2 new drug-related AEs associated with dupilumab that were not mentioned in the SmPC, including non-infectious conjunctivitis and meibomian gland dysfunction.

Our findings indicate that the incidence of eosinophilia associated with dupilumab treatment could be underestimated in the SmPC. The TREAT NL registry only reports eosinophilia as a drug-related AE if it was not pre-existent before treatment initiation. In our study, the incidence rate of eosinophilia was 11.9% ($n = 40$), implying that eosinophilia is a 'very common' (≥10%) undesirable effect instead of 'common' (≥1%–<10%). This is in line with the findings of two multicentre retrospective cohort studies that found that dupilumab-related eosinophilia was more common in real life compared to phase III trials.[30,31] In our study, only five cases of eosinophilia were reported in patients using other therapies than dupilumab, suggesting that the high rate of eosinophilia found in patients on dupilumab is indeed caused by the drug itself rather than active AD. It has been found that dupilumab-induced eosinophilia is often transient without clinical consequences and hypereosinophilia only occurs in a minority of patients.[32] In the TREAT NL cohort, the incidence rate of hypereosinophilia was 5.1%, resulting into treatment discontinuation in one patient. More research into dupilumab-induced (hyper)eosinophilia in AD patients is needed to provide recommendations on its management.

Ocular complaints arising during dupilumab treatment have been increasingly reported since its approval in 2017, with conjunctivitis being the most frequently described ocular AE.[33–35] However, studies often do not specify the type of conjunctivitis.[36] Similarly, the SmPC only mentions allergic conjunctivitis and infectious conjunctivitis. It is unclear whether dupilumab-associated conjunctivitis (DAC) is clinically captured by allergic conjunctivitis. Since DAC is not a MedDRA Preferred Term, we believe non-infectious conjunctivitis is the most suitable Preferred Term. Due to the use of unspecific terms, comparing ocular events to literature and the SmPC is challenging. Using more specific terms to describe ocular events associated with dupilumab can prompt early diagnosis. This is of importance since ocular AEs can lead to discontinuation of treatment and sometimes to long-term sequelae.[37] If, however, the Preferred Term allergic conjunctivitis is maintained for DAC, the resulting incidence rate of conjunctivitis related to dupilumab in our study is 10.1% (consisting of a total of 34 cases of conjunctivitis, allergic conjunctivitis and non-infectious conjunctivitis), equivalent to 'very common' (>10%). This indicates the incidence mentioned in the SmPC could be an underestimation of the actual real-life incidence, as it is grouped under 'common' (≥1%–<10%). Another study reports an even higher incidence of 26.1% for DAC.[38]

Other dupilumab-induced ocular AEs with higher incidence rates in the TREAT NL cohort compared to the SmPC included dry eyes and blepharitis. Various retrospective

TABLE 5 AEs possibly, probably, very likely or definitely related to systemic immunomodulating drugs (dupilumab, methotrexate, ciclosporin, mycophenolate mofetil, tralokinumab, baricitinib and upadacitinib) and incidence rates of AEs in the TREAT NL cohort compared to the incidence mentioned in the corresponding SmPCs.

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Ciclosporin					
Total number of AEs	16	5	11		
Type of severe AE					
Blood and lymphatic system disorders	1		1		
Eosinophilia	1		1	3.1%	*Not in SmPC*
Gastrointestinal disorders	2	1	1		
Abdominal pain	2	1	1	3.1%	≥1% to <10%
General disorders and administration site conditions	1		1		
Pyrexia	1		1	3.1%	≥1% to <10%
Immune system disorders	1	1			
Gout	1	1		3.1%	
Infections and infestations	2		2		
Eczema herpeticum	1		1	3.1%	*Not in SmPC*
Epididymitis	1		1	3.1%	*Not in SmPC*
Musculoskeletal and connective tissue disorders	1		1		
Myalgia	1		1	3.1%	≥1% to <10%
Nervous system disorders	4		4		
Headache	3		3	9.2%	≥10%
Paraesthesia	1		1	3.1%	≥1% to <10%
Skin and subcutaneous tissue disorders	2	2			
Body hair increased	2	2		6.1%	≥1% to <10%
Vascular disorders	2	1	1		
Hypertension	2	1	1	3.1%	≥10%
Methotrexate (oral)					
Total number of AEs	36	2	34		
Type of AE					
Blood and lymphatic system disorders	3		3		
Eosinophilia	3		3	8.1%	<0.01%
Gastrointestinal disorders	14		14		
Abdominal pain	3		3	8.1%	≥10%
Diarrhoea	3		3	8.1%	≥10%
Flatulence	1		1	2.7%	*Not in SmPC*
Nausea	4		4	10.8%	≥10%
Vomiting	2		2	5.4%	≥10%
General disorders and administration site conditions	6		6		
Fatigue	5		5	13.5%	≥1% to <10%
Malaise	1		1	2.7%	*Not in SmPC*
Hepatobiliary disorders	2	1	1		
Alanine aminotransferase increased	1		1	2.7%	≥10%
Raised liver function tests	1	1		2.7%	≥10%
Immune system disorders	1		1		
Drug hypersensitivity	1		1	2.7%	≥0.1% to <1%
Infections and infestations	2	1	1		
Erysipelas	1		1	2.7%	≥1% to <10%
Acute tonsillitis	1	1		2.7%	≥1% to <10%

TABLE 5 (Continued)

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Metabolism and nutrition disorders	3		3		
Abnormal loss of weight	1		1	2.7%	*Not in SmPC*
Decreased appetite	2		2	5.4%	≥10%
Nervous system disorders	3		3		
Headache	2		2	5.4%	≥10%
Dizziness	1		1	2.7%	≥10%
Reproductive system and breast disorders	1		1		
Erectile dysfunction	1		1	2.7%	<0.01%
Skin and subcutaneous tissue disorders	1		1		
Skin ulcer	1		1	2.7%	*Not in SmPC*
Vascular disorders	1		1		
Hypertension	1		1	2.7%	*Not in SmPC*
Methotrexate (subcutaneous)					
Total number of AEs	8	0	8		
Type of AE					
Blood and lymphatic system disorders	2		2		
Eosinophilia	1		1	21.2%	*Unknown*
Anaemia	1		1	21.2%	≥1% to <10%
Gastrointestinal disorders	4		4		
Diarrhoea	2		2	42.5%	≥1% to <10%
Nausea	2		2	42.5%	≥10%
Infections and infestations	1		1		
Campylobacter infection* * Captured as 'infections' in the SmPC	1		1	21.2%	≥1% to <10%
Nervous system disorders	1		1		
Mycophenolate mofetil					
Total number of AEs	1		1		
Type of AE					
Gastrointestinal disorders	1		1		
Nausea			1	31.0%	>10%
Dupilumab					
Total number of AEs	154	8	146		
Type of AE					
Blood and lymphatic system disorders	40		40		
Eosinophilia	40		40	11.9%	≥1% to <10%
Eye disorders	75	2	73		
Blepharitis	10		10	3.0%	≥0.1% to <1%
Conjunctivitis allergic	9	1	8	2.7%	≥1% to <10%
Dry eye	12		12	3.6%	≥0.1% to <1%
Ectropion	2		2	0.6%	*Not in SmPC*
Eye irritation	2		2	0.6%	*Not in SmPC*
Eye pruritus	3		3	0.9%	≥0.1% to <1%
Eyelid ptosis	1		1	0.3%	*Not in SmPC*
Eyelid skin dryness	1		1	0.3%	*Not in SmPC*
Lacrimation increased	2		2	0.6%	*Not in SmPC*
Meibomian gland dysfunction	5		5	1.5%	*Not in SmPC*
Meibomianitis	2		2	0.6%	*Not in SmPC*
Non-infectious conjunctivitis	20	1	19	6.0%	*Not in SmPC*
Ocular hyperaemia	3		3	0.9%	*Not in SmPC*

(Continues)

TABLE 5 (Continued)

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Photophobia	1		1	0.3%	*Not in SmPC*
Refraction disorder	1		1	0.3%	*Not in SmPC*
Trichiasis	1		1	0.3%	*Not in SmPC*
Gastrointestinal disorders	2		2		
Mouth ulceration			1	0.3%	*Not in SmPC*
Nausea	1		1	0.3%	*Not in SmPC*
General disorders and administration site conditions	4	1	3		
Fatigue	2		2	0.6%	*Not in SmPC*
Injection site reaction	2	1	1	0.6%	≥1% to <10%
Immune system disorders	2		2		
Drug hypersensitivity	1		1	0.3%	≥0.01% to <0.1%
Vaccination complication	1		1	0.3%	*Not in SmPC*
Infections and infestations					
Conjunctivitis	5	3	2	1.5%	≥1% to <10%
Fungal skin infection	1		1	0.3%	*Not in SmPC*
Herpes zoster	2		2	0.6%	*Not in SmPC*
Herpes virus infection	1		1	0.3%	*Not in SmPC*
Sinusitis	1		1	0.3%	*Not in SmPC*
Oral herpes	2		2	0.6%	≥1% to <10%
Metabolism and nutrition disorders	1		1		
Abnormal loss of weight	1		1	0.3%	*Not in SmPC*
Musculoskeletal and connective tissue disorders	6	1	5		
Arthralgia	6	1	5	1.8%	≥1% to <10%
Nervous system disorders	1		1		
Migraine	1		1	0.3%	*Not in SmPC*
Psychiatric disorders	1		1		
Depressed mood	1		1	0.3%	*Not in SmPC*
Skin and subcutaneous tissue disorders	10		10		
Alopecia	1		1	0.3%	*Not in SmPC*
Eczema	1		1	0.3%	*Not in SmPC*
Perioral dermatitis	2		2	0.6%	*Not in SmPC*
(Head and neck) erythema	5		5	1.5%	≥0.1% to <1%
Skin irritation	1		1	0.3%	*Not in SmPC*
Tralokinumab					
Total number of AEs	3		3		
Type of AE					
Eye disorders	2		2		
Lacrimation increased	1		1	53.9%	*Not in SmPC*
Ocular hyperaemia	1		1	53.9%	*Not in SmPC*
Infections and infestations	1		1		
Urinary tract infection	1		1	53.9%	*Not in SmPC*
Baricitinib					
Total number of AEs	1		1		
Type of AE					
Nervous system disorders	1		1		
Headache	1		1	25.7%	≥1% to <10%

TABLE 5 (Continued)

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Upadacitinib					
Total number of AEs	5	4	1		
Type of AE					
Infections and infestations	3	3			
Herpes virus infection	3	3		32.2%	≥1% to <10%
Nervous system disorders	1		1		
Headache	1		1	32.2%	≥1% to <10%
Respiratory, thoracic and mediastinal disorders	1	1			
Asthma (exacerbation)	1		1	32.2%	*Not in SmPC*

TABLE 6 Incidence rates of ocular AEs in the TREAT NL cohort that are possibly, probably, very likely, definitely related to dupilumab treatment, compared to the incidence mentioned in the SmPC.

	Number of cases	TREAT NL incidence rate (per patient year)	SmPC incidence
Total number of ocular AEs	80		
Eye disorders			
Blepharitis	10	3.0%	≥0.1% to <1%
Conjunctivitis allergic	9	2.7%	≥1% to <10%
Dry eyes	12	3.6%	≥0.1% to <1%
Ectropion	2	0.6%	*Not in SmPC*
Eye irritation	2	0.6%	*Not in SmPC*
Eye pruritus	3	0.9%	≥0.1% to <1%
Eyelid ptosis	1	0.3%	*Not in SmPC*
Eyelid skin dryness	1	0.3%	*Not in SmPC*
Lacrimation increased	2	0.6%	*Not in SmPC*
Meibomian gland dysfunction	5	1.5%	*Not in SmPC*
Meibomianitis	2	0.6%	*Not in SmPC*
Non-infectious conjunctivitis	20	6.0%	*Not in SmPC*
Ocular hyperaemia	3	0.9%	*Not in SmPC*
Photophobia	1	0.3%	*Not in SmPC*
Refraction disorder	1	0.3%	*Not in SmPC*
Trichiasis	1	0.3%	*Not in SmPC*
Infections and infestations			
Conjunctivitis	5	1.5%	≥1% to <10%

studies showed incidences of dupilumab-associated dry eyes ranging from 3.9% to 10%.[39–41] For blepharitis, even higher incidences of up to 22% have been reported.[42,43] Moreover, we found that meibomian gland dysfunction was a 'common' dupilumab-related AE, however, it is not mentioned in the SmPC. A recent study reported that meibomian gland dysfunction occurred in 25% of dupilumab users.[44] We believe that describing this AE in the SmPC of dupilumab would lead to more awareness and early therapeutic intervention prospects.

Ocular complaints including (blepharo-)conjunctivitis, dry eyes, eye pruritus, blurry vision, keratitis, meibomian gland dysfunction, limbus nodules and cicatricial ectropion can be covered under the umbrella term dupilumab-induced ocular surface disease (DIOSD).[1,45–47] A systematic review that included 2883 AD patients on dupilumab reports that DIOSD occurred in 13% of patients.[46] Supporting these findings, we found that DIOSD was reported in 15% of patients. Interestingly, DIOSD is not reported in asthma, chronic sinusitis or nasal polyps patients receiving dupilumab, suggesting that a disease-specific interaction exists.[48–50] Since ocular diseases such as conjunctivitis are more common in AD patients, pre-existent ocular disease could predispose to higher

rates of DIOSD.[47,51] As the risk of development of ocular comorbidities is disease severity-dependent, this is especially true for patients suffering from severe AD.[52] In our study, one patient with conjunctivitis and five patients with non-infectious conjunctivitis already experienced ocular complaints before treatment initiation, so these might be considered as dupilumab-exacerbated rather than dupilumab-induced.

Dupilumab-induced head and neck erythema (i.e. dupilumab facial redness) has been reported in 5.4%–29% of patients by other studies.[53,54] This supports our finding that dupilumab-induced head and neck erythema have a higher real-life incidence compared to the SmPC. The pathogenesis is still unclear and despite several speculations, further studies are indicated to investigate this AE.[55,56]

Lastly, we found a higher incidence rate of fatigue related to methotrexate (oral) treatment than mentioned in the SmPC ('very common' vs 'common'). However, as fatigue is also a common symptom of AD itself, due to active disease and sleep loss, it may be challenging to distinguish its cause. This AE has not yet been extensively studied in AD patients, but a recent prospective study on patient-reported fatigue and nausea related to methotrexate in rheumatoid- and psoriatic arthritis patients found even higher rates of fatigue, reported by 46% of patients, suggesting the incidence may indeed be underestimated in the SmPC of methotrexate.[57]

The major strength of this study is the use of RWD derived from the daily practice of 266 AD patients on various treatments, with a total follow-up of 422 patient years. The external validity is likely to be high, considering the fact the TREAL NL registry consists of both adult- and paediatric patients, including those with comorbidities. However, the small number of patients on treatments other than dupilumab, oral methotrexate and ciclosporin can be considered as a limitation, as the calculated incidence rates of AEs related to these treatments may be an over- or underestimate and cannot be adequately compared to the corresponding SmPCs. Furthermore, due to the prominent enrolment of patients treated with dupilumab, there is a possibility that an unintentional exaggeration of dupilumab's adverse effects in comparison to other agents may have been depicted.

Moreover, the fact that only AEs of severe nature were reported might as well be a limitation of this study. This likely caused the estimated incidence rates of the reported AEs to be an underestimation of the actual incidences. This does not apply to dupilumab-related eosinophilia and ocular AEs, as these are AESIs and were always reported, independent of their severity. However, baseline eosinophil count was not determined in patients starting dupilumab in University Hospital Ghent, which could have led to an underestimation of the incidence of dupilumab-induced eosinophilia in this centre. In addition, mild ocular AEs might not always be adequately diagnosed, since these patients did not always visit an ophthalmologist.

Another limitation might be that relatedness to the treatment of AEs was assessed by a physician at the moment of occurrence. As recent safety studies on more novel treatments, like dupilumab, have provided new insights not present at the time of study initiation, relatedness may have been misinterpreted or interpreted incompletely among physicians during earlier study visits. Moreover, due to these new insights, the list of AESIs collected in the TREAT NL registry has changed over time, which may have led to underreporting of AESIs.

To standardize the assessment of drug-relatedness of AEs in the future, we will start using the Naranjo Scale (the AE Probability Scale).[58]

This study illustrates that real-world reported AEs captured in AD patient registries can potentially add information on the estimated incidence of AEs to the SmPC, and can subsequently benefit clinical decision aids. Current SmPCs might need an update which will contribute to safer pharmacotherapy. Results from this study will be shared with the Netherlands Pharmacovigilance Centre Lareb. Subsequently, data can be retrieved by third parties and possibly shared with databases from the EMA (Eudravigilance) and World Health Organization VigiBase. More collection of RWD is needed to provide new insights on the safety of treatments that are underrepresented in this study, including tralokinumab, baricitinib, upadacitinib and abrocitinib. Future studies using data derived from the TREAT NL registry combined with RWD from other registries within the TREAT Registry Taskforce will provide even more information on (rare) AEs associated with immunomodulating therapy in AD patients.

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CONFLICT OF INTEREST STATEMENT

A.H. Musters has no conflicts of interest. F.L. van Lookeren has no conflicts of interest. L.F. van der Gang has no conflicts of interest. M.A. Middelkamp-Hup has done consultancies for Sanofi and Leo Pharma. She is one of the main investigators of the TREAT NL registry. A.L. Bosma has no conflicts of interest. N.T. Jessurun has no conflicts of interest. H. Lapeere has participated in advisory boards from Leo Pharma, Abbvie, Pfizer, Galderma and Sanofi. A.L. Nguyen has done consultancies for Leo-Pharma. She is one of the investigators of the TREAT NL registry. W.

Ouwerkerk has no conflicts of interest. S. de Schepper has no conflicts of interest. L.A.A. Gerbens is one of the main investigators of the TREAT NL registry. She has no further conflicts of interest. P.I. Spuls received departmental independent research grants from pharmaceutical industries since December 2019 for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the photo- and systemic therapy atopic eczema registry (TREAT NL) for adults and children.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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