Adverse events associated with dupilumab in the WHO pharmacovigilance database.

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Dr. Drucker has received compensation from the British Journal of Dermatology (reviewer and Section Editor), American Academy of Dermatology (guidelines writer) and National Eczema Association (grant reviewer). He has been a paid consultant for Canadian Agency for Drugs and Technology in Health. He has received honoraria from CME Outfitters. He is a contributing member to the Harmonizing Outcome Measures for Eczema (HOME) initiative. The other authors have no other conflict of interest to disclose

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Atopic dermatitis, eczema, atopic eczema, dupilumab, pharmacovigilance, adverse events

Dupilumab is a monoclonal antibody targeting the IL4/IL13 pathway approved to treat atopic dermatitis. Dupilumab has a favourable safety profile in randomized controlled trials and observational cohorts, but has been associated with a number of adverse events, including exacerbation of atopic dermatitis, eye disorders, or eosinophilia.[1,2] Nevertheless, data are limited by short time frames. In order to assess adverse events associated with dupilumab, we conducted a pharmacovigilance study using Vigibase, the WHO global pharmacovigilance database.

We searched Vigibase and included all reports with dupilumab as suspected cause from January 1st 2016 to October 15th 2020. Adverse events were classified according to the MedDRA classification, grouped into the 27 branches of the System Organ Class.[3] To identify adverse events associated with dupilumab, we used the information component (IC), an indicator for disproportionate reporting, and IC_{025}, the lower limit of its 95% credibility interval. $IC_{025>0}$ is the statistical significance threshold used in Vigibase **(supplementary methods)**, meaning that the adverse event is likely associated with dupilumab.[4] The higher is the IC_{025}, the stronger is the association. We included physician reports in the primary analysis and overall reports in the sensitivity analysis.

Among the 4,894 physician reports, a total of 11,751 events (including 1,326 different adverse events) were reported. The median age was 44 (IQR: 28-57) years and 1,884 patients were female (38%) (**Table S1**). IC_{025} was positive for 168/1,326 (14%) different adverse events. Skin disorders displayed 53 (32%) associated adverse events, mostly related to atopic dermatitis (n=15, IC_{025} ranging from 0.6 to 6.6), alopecia areata (IC_{025} 4.1) and psoriasis-like eruptions (IC_{025} 2.2). Eye disorders displayed 35 (21%) associated adverse events, mainly related to conjunctivitis and keratitis symptoms (**Table S2**), infections and infestations, 14 adverse events (8%), mainly related to herpes infections (**Table S3**). Musculoskeletal disorders displayed 8 adverse events (5%), blood and lymphatic disorders 5 adverse events, (3%) and immune disorders 5 adverse events (3%), including serum sickness (IC_{025} 3.9) (**Figure and Table**). Other adverse events mostly consisted in local reactions (**Table S4-S6**). Overlapping reports between skin, eye, infectious or musculoskeletal disorders were rare (less than 10% of reports, **Figure S2**). Skin and eye disorders were more frequent among patients using dupilumab for atopic dermatitis, whereas musculoskeletal disorders were more frequent among patients with asthma (**Figure S3**).

In this study, dupilumab was most commonly associated with skin, ophthalmologic, musculoskeletal and skin infectious adverse events, and rare adverse events, such as serum

sickness. We found no association with serious infections, vascular events, psychiatric disorders or cancer, with the exception of cutaneous T cell lymphoma. Nevertheless, this association could represent cases of mycosis fungoides originally misdiagnosed as atopic dermatitis. Conversely, Espinosa et al reported a progression of mycosis fungoides after treatment with dupilumab, suggesting that Th2 response might be important to control mycosis fungoides.[5] Likewise, because pharmacovigilance databases are built on spontaneous reporting, we were unable to assess incidence of and risk factors for adverse events. Several adverse events reported in our study might be a consequence of inverse causality bias and observer bias, particularly flares of pre-existing atopic dermatitis.

With few serious adverse events in routine clinical use, we confirm dupilumab favorable safety observed in clinical trials, supporting the absence of additional costs that could burden the health economic evaluation, such as the good overall benefit/risk ratio of dupilumab.

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143 **Table** Skin and subcutaneous tissue disorders, musculoskeletal disorders, blood and lymphatic
144 disorders and immune disorders associated with dupilumab

Adverse events	**Number of physician reports**	**IC_{025} physician**	**Number of overall reports**	**IC_{025}**
Dermatitis atopic	193	6.6	3015	7.6
Eczema	140	3.8	1461	4.9
Dermatitis	84	3.4	1267	5.0
Alopecia areata	34	4.1	55	3.3
Skin exfoliation	81	2.8	1146	3.0
Cut T-cell lymphoma	12	2.8	19	2.8
Skin plaque	22	2.7	41	1.5
Skin papilloma	12	2.3	32	1.9
cRosacea	16	2.3	35	1.5
Pain of skin	17	2.3	94	0.5
Dermatitis psoriasiform	12	2.2	16	1.4
Skin mass	14	2.1	87	2.7
Lichenification	6	2.0	38	5.1
Neurodermatitis	8	1.9	32	3.3
Erythema	261	1.8	1568	1.3
Dry skin	44	1.8	1440	2.7
Perioral dermatitis	6	1.8	10	2.3
Skin lesion	28	1.7	84	1.1
Seborrheic dermatitis	8	1.7	22	2.3
Sensitive skin	5	1.4	36	1.3
Hair growth abnormal	7	1.4	26	0.6
Alopecia	95	1.3	615	0.6
Lichen planus	7	1.3	13	1.1
Skin weeping	4	1.2	32	4.5
Skin disorder	21	1.2	200	2.1
Hyperkeratosis	8	1.2	18	0.5
Swelling face	35	1.1	192	0.6
Skin irritation	11	1.0	227	1.0
Vitiligo	7	1.0	9	0.3
Papule	11	1.0	35	0.9
Skin discolouration	21	1.0	272	1.7
Rash erythematous	49	0.8	255	0.6
Discomfort	19	0.8	334	2.0
Rash pustular	10	0.8	28	0.5
Rash macular	21	0.6	283	1.7
Exfoliative rash	5	0.6	21	1.7
Psoriasis	46	0.6	197	0.1
Photosensitivity reaction	15	0.6	88	1.3
Scratch	7	0.6	112	2.5
Blister	21	0.5	194	0.9
Skin tightness	4	0.4	37	1.5
Alopecia universalis	3	0.4	3	0.1
Nodular rash	3	0.4	3	0.1
Alopecia totalis	3	0.4	5	0.8
Erythrodermic psoriasis	3	0.3	4	0.3
Skin haemorrhage	6	0.3	175	3.3
Pustule	6	0.3	23	0.7
Pruritus	223	0.3	3502	0.9

Burning sensation	20	0.3	177	0.4
Palmoplantar keratoderma	3	0.2	4	0.1
Rash	290	0.1	3603	1.0
Scab	5	0.0	84	2.0
Pustular psoriasis	4	0.0	4	0.1
Musculoskeletal and connective tissue disorders				
Arthralgia	255	1.7	1195	1.0
Joint stiffness	17	1.4	70	0.9
Enthesopathy	5	1.3	10	2.1
Arthritis	24	0.7	95	0.0
Joint swelling	31	0.6	187	0.6
Foot operation	4	0.5	12	0.5
Seronegative arthritis	3	0.4	5	1.3
Epicondylitis	3	0.1	6	0.4
Blood and lymphatic system disorders & Immune system disorders				
Eosinophil count increased	71	4.4	115	3.6
Serum sickness	27	3.9	44	3.1
Serum sickness-like reaction	15	3.5	22	3.1
Eosinophilia	114	3.4	133	2.5
Erythema nodosum	15	2.4	30	2.2
Lymphadenopathy	34	1.3	143	1.2
EGPA	5	1.3	9	1.0
Lymphocytic infiltration	4	1.1	6	1.3
Food allergy	4	0.3	22	1.0
Seasonal allergy	5	0.1	50	1.3

Cut T-cell lymphoma: Cutaneous T cell lymphoma

IC: Information Component; IC_{025} is the lower limit of the 95% credibility interval of IC. A positive IC_{025} is the statistical threshold used in Vigilyze.

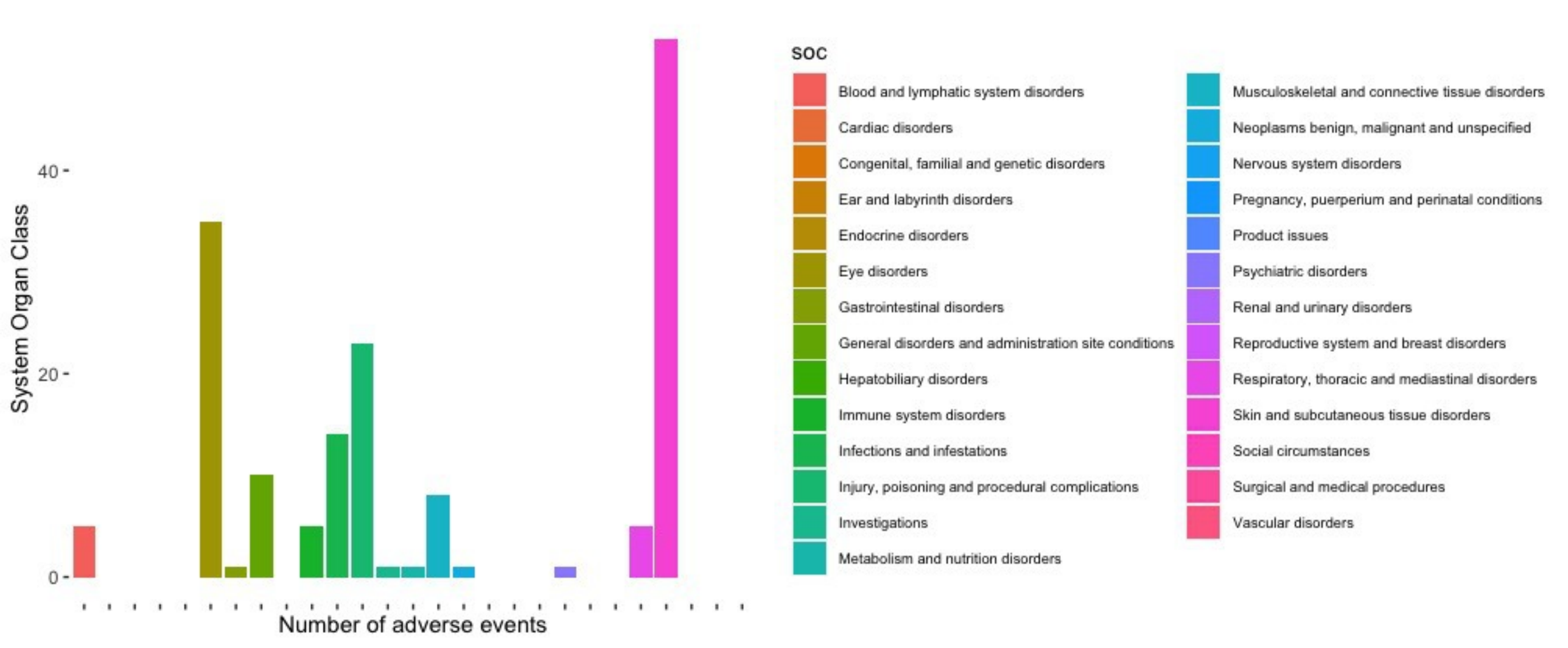
EGPA: Eosinophilic granulomatous with polyangeitis

IC: Information Component; IC_{025} is the lower limit of the 95% credibility interval of IC. A positive IC_{025} is the statistical threshold used in Vigilyze.

Legend

Figure Number of Adverse events with positive IC_{025} according to the System Organ Class, in the primary analysis.

SOC: System Organ Class; AEs: Adverse events; IC: Information Component; IC_{025} is the lower limit of the 95% credibility interval of IC. A positive IC_{025} is the statistical threshold used in Vigilyze.aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa


System Organ Class
40
20
0
Number of adverse events
SOC
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Product issues
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social circumstances
Surgical and medical procedures
Vascular disorders