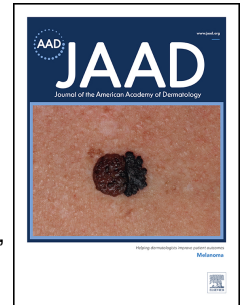


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Thomas Bettuzzi, MD, Aaron Drucker, MD, ScM, Delphine Staumont-Sallé, MD, PhD,
Kevin Bihan, PharmD, Bénédicte Lebrun-Vignes, MD, Emilie Sbidian, MD, PhD



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Adverse events associated with dupilumab in the WHO pharmacovigilance database

Thomas Bettuzzi, MD,^{1,2} Aaron Drucker, MD, ScM,^{3,4} Delphine Staumont-Sallé, MD, PhD,⁵ Kevin Bihan, PharmD,⁶ Bénédicte Lebrun-Vignes, MD,⁶ Emilie Sbidian, MD, PhD^{1,2,7}

¹ Service de Dermatologie, AP-HP, Hôpital Henri Mondor, F-94010 Créteil, France

² EpiDermE, Univ Paris Est Créteil, F-94010 Créteil, France

³. Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Canada

⁴ Women's College Research Institute and Department of Medicine, Women's College

Hospital, Toronto, Canada

⁵ Service de Dermatologie, Centre Hospitalo-Universitaire de Lille, Université de Lille 2,

Lille, France

⁶ Centre Régional de Pharmacovigilance, Service de Pharmacologie clinique, Hôpital Pitié-

Salpêtrière, AP-HP

⁷ INSERM, Centre d'Investigation Clinique 1430, F-94010 Créteil, France

Corresponding author:

Thomas Bettuzzi, MD, MPH

thomasbettuzzi@gmail.com

51 avenue du Maréchal Lattre de Tassigny

94000 Créteil

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Conflict of Interest:

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

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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 IC₀₂₅, 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 IC₀₂₅, 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**). IC₀₂₅ 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, IC₀₂₅ ranging from 0.6 to 6.6), alopecia areata (IC₀₂₅ 4.1) and psoriasis-like eruptions (IC₀₂₅ 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 (IC₀₂₅ 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.

References

1. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. doi:10.1056/NEJMoa1610020
2. Faiz S, Giovannelli J, Podevin C, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. *J Am Acad Dermatol*. 2019;81(1):143-151. doi:10.1016/j.jaad.2019.02.053
3. Bousquet C, Lagier G, Lillo-Le Louët A, Le Beller C, Venot A, Jaulent M-C. Appraisal of the MedDRA Conceptual Structure for Describing and Grouping Adverse Drug Reactions: *Drug Saf*. 2005;28(1):19-34. doi:10.2165/00002018-200528010-00002
4. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. 1998;54(4):315-321. doi:10.1007/s002280050466
5. Espinosa ML, Nguyen MT, Aguirre AS, et al. Progression of cutaneous T-cell lymphoma after dupilumab: Case review of 7 patients. *J Am Acad Dermatol*. 2020;83(1):197-199. doi:10.1016/j.jaad.2020.03.050

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
Rosacea	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; $IC_{0.25}$ is the lower limit of the 95% credibility interval of IC. A positive $IC_{0.25}$ is the statistical threshold used in Vigilyze.

EGPA: Eosinophilic granulomatous with polyangeitis

IC: Information Component; $IC_{0.25}$ is the lower limit of the 95% credibility interval of IC. A positive $IC_{0.25}$ 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.

