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Thomas Bettuzzi, Aaron Drucker, Delphine Staumont, Kevin Bihan,  
Bénédicte Lebrun-Vignes, Emilie Sbidian

### ► To cite this version:

Thomas Bettuzzi, Aaron Drucker, Delphine Staumont, Kevin Bihan, Bénédicte Lebrun-Vignes, et al.. Adverse events associated with dupilumab in the WHO pharmacovigilance database.. Journal of The American Academy of Dermatology, 2021, Journal of The American Academy of Dermatology, 86 (2), pp.P431-433. 10.1016/j.jaad.2021.09.050 . hal-04419621

**HAL Id: hal-04419621**

**<https://hal.univ-lille.fr/hal-04419621v1>**

Submitted on 22 Jul 2024

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1 **Adverse events associated with dupilumab in the WHO pharmacovigilance database**

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3 Thomas Bettuzzi, MD,<sup>1,2</sup> Aaron Drucker, MD, ScM,<sup>3,4</sup> Delphine Staumont-Sallé, MD, PhD,<sup>5</sup>  
4 Kevin Bihan, PharmD,<sup>6</sup> Bénédicte Lebrun-Vignes, MD,<sup>6</sup> Emilie Sbidian, MD, PhD<sup>1,2,7</sup>

5  
6 <sup>1</sup> Service de Dermatologie, AP-HP, Hôpital Henri Mondor, F-94010 Créteil, France

7 <sup>2</sup> EpiDermE, Univ Paris Est Créteil, F-94010 Créteil, France

8 <sup>3</sup>. Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Canada

9 <sup>4</sup> Women's College Research Institute and Department of Medicine, Women's College  
10 Hospital, Toronto, Canada

11 <sup>5</sup> Service de Dermatologie, Centre Hospitalo-Universitaire de Lille, Université de Lille 2,  
12 Lille, France

13 <sup>6</sup> Centre Régional de Pharmacovigilance, Service de Pharmacologie clinique, Hôpital Pitié-  
14 Salpêtrière, AP-HP

15 <sup>7</sup> INSERM, Centre d'Investigation Clinique 1430, F-94010 Créteil, France

16

17 **Corresponding author:**

18 Thomas Bettuzzi, MD, MPH

19 thomasbettuzzi@gmail.com

20 51 avenue du Maréchal Lattre de Tassigny

21 94000 Créteil

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24 **Word count:** 500

25 **References:** 5

26

27 **Tables:** 1

28 **Supplementary Table:** 6

29

30 **Figures:** 1

31 **Supplementary Figures:** 1

32 **Mendeley Link for Supplemental Material:**

33 <https://data.mendeley.com/datasets/bf5vnbh33r/1>

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36 **Conflict of Interest:**

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

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45 **Funding:** none

46 **Key words**

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

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

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

67 Among the 4,894 physician reports, a total of 11,751 events (including 1,326 different  
68 adverse events) were reported. The median age was 44 (IQR: 28-57) years and 1,884 patients  
69 were female (38%) (**Table S1**). IC<sub>025</sub> was positive for 168/1,326 (14%) different adverse  
70 events. Skin disorders displayed 53 (32%) associated adverse events, mostly related to atopic  
71 dermatitis (n=15, IC<sub>025</sub> ranging from 0.6 to 6.6), alopecia areata (IC<sub>025</sub> 4.1) and psoriasis-like  
72 eruptions (IC<sub>025</sub> 2.2). Eye disorders displayed 35 (21%) associated adverse events, mainly  
73 related to conjunctivitis and keratitis symptoms (**Table S2**), infections and infestations, 14  
74 adverse events (8%), mainly related to herpes infections (**Table S3**). Musculoskeletal  
75 disorders displayed 8 adverse events (5%), blood and lymphatic disorders 5 adverse events,  
76 (3%) and immune disorders 5 adverse events (3%), including serum sickness (IC<sub>025</sub> 3.9)  
77 (**Figure and Table**). Other adverse events mostly consisted in local reactions (**Table S4-S6**).  
78 Overlapping reports between skin, eye, infectious or musculoskeletal disorders were rare (less  
79 than 10% of reports, **Figure S2**). Skin and eye disorders were more frequent among patients  
80 using dupilumab for atopic dermatitis, whereas musculoskeletal disorders were more frequent  
81 among patients with asthma (**Figure S3**).

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

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

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

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

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

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

145 Cut T-cell lymphoma: Cutaneous T cell lymphoma  
146 IC: Information Component; IC<sub>0.25</sub> is the lower limit of the 95% credibility interval of IC. A positive IC<sub>0.25</sub> is the  
147 statistical threshold used in Vigilyze.  
148 EGPA: Eosinophilic granulomatous with polyangeitis  
149 IC: Information Component; IC<sub>0.25</sub> is the lower limit of the 95% credibility interval of IC. A positive IC<sub>0.25</sub> is the  
150 statistical threshold used in Vigilyze.  
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**Legend**

**Figure** Number of Adverse events with positive  $IC_{0.25}$  according to the System Organ Class, in the primary analysis.

SOC: System Organ Class; AEs: Adverse events; 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.aa

