



**HAL**  
open science

## Immediate hypersensitivity to dupilumab: A French case series

Romain Lemery, Claire Cariou, Anne-Sophie Darrigade, Cécile Rochefort-Morel, Priscille Carvalho-Lallement, Billal Tedbirt, Elisabeth Polard, Sylvie Picard, Sandrine Bergeron, Paola Sanchez-Pena, et al.

► **To cite this version:**

Romain Lemery, Claire Cariou, Anne-Sophie Darrigade, Cécile Rochefort-Morel, Priscille Carvalho-Lallement, et al.. Immediate hypersensitivity to dupilumab: A French case series. *Journal of Allergy and Clinical Immunology: In Practice*, 2023, 11 (8), pp.2608-2610. 10.1016/j.jaip.2023.04.043 . hal-04244590

**HAL Id: hal-04244590**

**<https://univ-rennes.hal.science/hal-04244590>**

Submitted on 30 Nov 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Immediate hypersensitivity to dupilumab: a French case series**

2

3 **Authors:** Romain Lemery<sup>1</sup>, MD; Claire Cariou<sup>1,2</sup>, MD; Anne-Sophie Darrigade<sup>3</sup>, MD ;  
4 Cécile Rochefort-Morel<sup>2</sup>, MD; Priscille Carvalho-Lallement<sup>4</sup>, MD; Billal Tedbirt<sup>4</sup>, MD;  
5 Elisabeth Polard<sup>5</sup>, PharmD; Sylvie Picard<sup>5</sup>, PharmD; Sandrine Bergeron<sup>6</sup>, PharmD ;  
6 Paola Sanchez-Pena<sup>7</sup>, PharmD; Alain Dupuy, MD, PhD<sup>1,8</sup>; Louise Triquet<sup>5</sup>, PharmD ;  
7 Catherine Droitcourt<sup>1,8</sup>, MD, PhD

8

9 **Affiliations:**

10 <sup>1</sup>Dermatology Department, Rennes University Medical Center, F-35000 Rennes, France

11 <sup>2</sup>Department of Pulmonology and Allergology, Rennes University Medical Center, F-  
12 35000 Rennes, France

13 <sup>3</sup>Dermatology Department, Bordeaux University Medical Center, F-33000 Bordeaux,  
14 France

15 <sup>4</sup>Dermatology Department, Rouen University Medical Center, F-76000 Rouen, France

16 <sup>5</sup>Regional Pharmacovigilance Center, Rennes University Medical Center, F-35000  
17 Rennes, France

18 <sup>6</sup>Regional Pharmacovigilance Center, Lille University Medical Center, F-59000 Lille,  
19 France

20 <sup>7</sup>Regional Pharmacovigilance Center, Bordeaux University Medical Center, F-33000  
21 Bordeaux, France

22 <sup>8</sup>Univ Rennes, INSERM, EHESP, Irset (Institut de recherche en santé, environnement et  
23 travail) – UMR\_S 1085, F-35000 Rennes, France

24 **Corresponding author:**

25 Dr Catherine Droitcourt, Department of Dermatology, University Hospital Centre of

26 Rennes, 2 Rue Henri le Guilloux, F-35000 Rennes, France, mailto:

27 [catherine.droitcourt@chu-rennes.fr](mailto:catherine.droitcourt@chu-rennes.fr).

28 Tel : + 33-299-284-349

29

30 **Financial disclosure:** The authors have no financial relationships relevant to this article  
31 to disclose.

32

33 **Conflict of interest:** The authors have no conflicts of interest to disclose.

34 **Funding:** This research did not receive any specific funding from agencies or

35 organizations in the public, commercial, or not-for-profit sectors

36 **Key words:** hypersensitivity, anaphylaxis, dupilumab, atopic dermatitis

37 **Words:** 1070/1000

38 **Figures / Tables:** 2

39 **References:** 9

40

41 **Authorship:** RL, CC, and CD designed the study and wrote the manuscript. ASD, PCL,

42 LT, SB, and PSP contributed to the data collection. All authors read and approved the

43 final manuscript.

44

45 Clinical implications box

46 Dupilumab immediate hypersensitivity is rarely described in pivotal studies : we report  
47 two cases of grade I and II immediate allergic reactions to dupilumab proven by positive  
48 IDTs. Three additional cases from the French pharmacovigilance database are  
49 described.

50

51 Dupilumab is a human monoclonal antibody against interleukin (IL)4 receptor alpha. It  
52 inhibits IL-4 and IL-13 *in vivo*. In the European Union, subcutaneously administered  
53 dupilumab has been approved for moderate-to-severe atopic dermatitis (AD),  
54 uncontrolled inflammatory/eosinophilic asthma in adults, adolescents and children aged  
55 six and over, and chronic rhinosinusitis with nasal polyposis in adults.

56 Dupilumab's safety profile has been described in clinical trials and real-life studies; the  
57 most frequent adverse events are injection-site reactions, conjunctivitis,  
58 blepharoconjunctivitis, and blood hypereosinophilia which is typically transient.

59 Here, we report on two adults who experienced immediate hypersensitivity reactions  
60 after subcutaneous injections of dupilumab for an indication of AD. Furthermore, we  
61 identified three cases of immediate hypersensitivity reactions notified in the French  
62 pharmacovigilance database (FPVD) between 2018 and 2022. All five patients provided  
63 informed consent to the publication of their personal medical data.

64

65 A 27-year-old woman was started on Dupilumab (Dupixent®, Sanofi, Paris, France) for  
66 severe AD. She experienced rhinitis within an hour of each the first five subcutaneous

67 injections of Dupilumab (dose: 300 mg), and then facial oedema, generalized urticaria,  
68 vomiting, and dizziness within a minute of the sixth injection (dose: 300 mg). The signs  
69 and symptoms resolved with self-administration of desloratadine, followed by treatment  
70 with intravenous corticosteroids and fluids. The basal serum tryptase level was normal  
71 (5.3 µg/l). Grade II immediate hypersensitivity to dupilumab was diagnosed.

72 Skin tests were performed four months after the reaction. Skin prick tests (SPTs) with  
73 undiluted dupilumab (150 mg/ml) and undiluted excipient polysorbate-80 contained in  
74 Dupixent® (PS80, associated with hypersensitivity reactions) were both negative. An  
75 intradermal test (IDT) of undiluted dupilumab was positive (immediate reading at 15  
76 minutes: mean wheal diameter of 12 mm with erythema, vs 4 mm for initial wheal). She  
77 received only doses of the SARS-CoV-2 Pfizer- BioNTech vaccine (Comirnaty®)  
78 containing PEG without any reaction, which couldn't rule out PS80 hypersensitivity.  
79 Hence, IDTs with PS80-containing Kenacort (4 mg/mL) were conducted (pure and  
80 diluted 0:10 and 0:100) and were negative. For comparison, IDTs with DUPIXENT®  
81 were conducted in nine healthy controls (members of the department's medical staff)  
82 and showed an irritative reaction with pure formulation in 5/9 cases, possibly due to  
83 potent irritative PS80.

84

85 A 59-year-old man was treated with dupilumab for severe AD. He experienced  
86 injection-point urticaria and then generalized urticaria within hours of the fourth  
87 subcutaneous injection of dupilumab (dose: 300 mg). The signs and symptoms resolved  
88 spontaneously but recurred after the fifth and sixth subcutaneous injections of

89 dupilumab and self-resolved each time. Grade I immediate hypersensitivity to  
90 dupilumab was diagnosed clinically, and the treatment was permanently discontinued.

91 An SPT with undiluted dupilumab (150 mg/ml) was negative (Figure 1) and an IDT test  
92 with dupilumab diluted 1:100 was positive (immediate reading at 15 minutes: mean  
93 wheal diameter of 13 mm at 15 minutes with erythema vs 4 mm for initial wheal).  
94 Intradermal tests with PS80-containing Kenacort (4 mg/mL) were conducted (pure and  
95 diluted 0:10 and 0:100) and were negative. Furthermore, the patient had received a first  
96 dose of the AstraZeneca- vaccine (Vaxzevria® containing PS80) and a second dose of  
97 the SARS- CoV- 2 Pfizer- BioNTech mRNA- vaccine (Comirnaty® containing PEG)  
98 without any reaction.

99 The characteristics of the cases notified in the FPVD are summarized in Table 1.

100

101 We observed two cases of immediate hypersensitivity to dupilumab; the reaction's  
102 allergic nature was evidenced by positive IDTs. We also identified three additional  
103 cases in the FPVD.

104 Although monoclonal antibodies are usually considered to be safe, adverse reactions are  
105 sometimes reported several years after market authorization. Hypersensitivity reactions  
106 are less frequent with fully humanized antibodies: for example, in a retrospective study  
107 of data from the US Food and Drug Administration's Adverse Event Reporting System,  
108 statistically significant links to anaphylaxis were observed for omalizumab and  
109 mepolizumab but not dupilumab (1). In most cases, the mechanisms of hypersensitivity  
110 to biologics have not been extensively studied or characterized in detail. However,  
111 direct  $\beta$ -type (IgE- or immune-complex-mediated) hypersensitivity to a therapeutic

112 protein or excipient is often suspected, as described by Pichler *et al.* (2). Although  
113 hypersensitivity to polysorbate (an excipient is found in around 70% of monoclonal  
114 antibody formulations) is well known, reports of direct hypersensitivity to the active  
115 antibody are much less common.

116 Dupilumab hypersensitivity is described as being very rare in the French and European  
117 summaries of product characteristics; indeed, only one case of anaphylaxis (with no  
118 further details provided) was reported during the pivotal SOLO CONTINUE study (3),  
119 with another case reported in the asthma development program(4). Horisberger (5) then  
120 reported on a case of a grade II hypersensitivity reaction (nausea, dyspnea, and  
121 angioedema) starting minutes after the 13<sup>th</sup> injection of dupilumab in a 22-year-old man  
122 treated for AD and asthma. The signs and symptoms resolved after the administration of  
123 intramuscular epinephrine, inhaled beta-2 agonists, and unspecified corticosteroids and  
124 antihistamines. An SPT with undiluted dupilumab was negative but IDTs for both PS80  
125 and 1:100 diluted dupilumab were positive. Given the presence of dyspnea and a peak-  
126 flow decrease after the IDT, PS80 was considered to be responsible for this grade II  
127 reaction.

128 Furthermore, eight cases of isolated, dupilumab-induced urticaria were observed in  
129 pivotal studies (3). Ludriksone *et al.*(6) reported on a 39-year-old woman with AD who  
130 developed injection-point urticaria (IPU) within 1 or 2 hours of each of the 10<sup>th</sup> to 18<sup>th</sup>  
131 dupilumab injections; the treatment was then discontinued. The IDT for dupilumab was  
132 positive (immediate test reading, dilution status not available) but the IDT for PS80  
133 (undiluted, and 1:10,000 to 1:10 dilutions) was negative, prompting a diagnosis of true  
134 dupilumab hypersensitivity. Three other cases of immediate IPU have been reported,  
135 with negative IDTs and SPTs after 20 min, 12 h and 24 h for both dupilumab and PS80

136 (the latter's dilution was not reported) (7,8). It is noteworthy that dupilumab treatment is  
137 sometimes pursued after the occurrence of IPU, which is considered to be a nonserious  
138 adverse reaction. In contrast, immediate hypersensitivity is considered to be serious and  
139 leads to discontinuation of the dupilumab treatment (8).

140 A case of face and hand angioedema recurring over several months after dupilumab  
141 injections was observed in a 12-year-old girl with AD and asthma (9). The angioedema  
142 appeared within 24 hours of each injection but no tests were performed.

143 In summary, we detail two cases of immediate hypersensitivity to dupilumab and  
144 describe several additional cases of type 1 hypersensitivity reaction, an adverse reaction  
145 very rarely described in the pivotal studies. Allergy work-up (including IDTs, notably)  
146 might be useful for differentiating between sensitization to dupilumab and sensitization  
147 to PS80.

148

#### 149 **Acknowledgements**

150 The authors thank Dr David Fraser (Biotech Communication SAL, Ploudalmézeau,  
151 France) for editorial assistance.

#### 152 **References**

- 153 1. Li L, Wang Z, Cui L, Xu Y, Guan K, Zhao B. Anaphylactic risk related to  
154 omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. *Clin Transl*  
155 *Allergy*. 2021 Jun.11(4).
- 156 2. Pichler WJ. Adverse side-effects to biological agents. *Allergy*. 2006  
157 Aug;61(8):912–20.
- 158 3. Worm M, Simpson EL, Thaçi D, Bissonnette R, Lacour JP, Beissert S, et al.  
159 Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial



- 160 Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical  
161 Trial. *JAMA Dermatol.* 2020 Feb 1;156(2):131.
- 162 4. Deeks ED. Dupilumab: A Review in Moderate to Severe Asthma. *Drugs.* 2019  
163 Nov;79(17):1885–95.
- 164 5. Horisberger A. Hypersensitivity reaction following dupilumab injection due to  
165 excipient polysorbate-80. *Swiss Medical Weekly;* 2019.
- 166 6. Ludriksone L, Elsner P, Schliemann S. Acquired hypersensitivity to dupilumab:  
167 first case report. *J Eur Acad Dermatol Venereol.* 2019 Dec;33(12).
- 168 7. Mastorino L, Ortoncelli M, Virginia B, Rolla G, Avallone G, Cavaliere G, et al.  
169 Dupilumab-induced Urticaria. *Dermatol Ther.* 2021;34(6):e15117.
- 170 8. Xu J, Shih J, Kalangara M. Delayed onset localized urticarial reactions to  
171 Dupilumab. *J Allergy Clin Immunol.* 2021 Feb;147(2):AB12.
- 172 9. Fritz AL, Lacy FA, Morrell DS. Angioedema: A potential complication of  
173 dupilumab in atopic dermatitis. *Pediatr Dermatol.* 2021 Jan;38(1):237–8.

174

175

176

177

178

179

180

181 **Tables and Figures**

182 **Table 1:** Characteristics of immediate hypersensitivity reactions to dupilumab reported  
183 in the FPVD

184 **Figure 1: Skin test results in case 2.** Note the positive IDT with 1:100 dilution

185

**Table 1:** Characteristics of immediate hypersensitivity reactions to dupilumab reported in the FPVD.

	Age	Sex	Medical history	Clinical details (injection number, time interval, signs and symptoms)	Ring and Messmer grade	Treatment of the anaphylactic reaction	SARS-CoV-2 vaccines	Skin tests
<b>Case 3</b>	78	Male	Atopic dermatitis of the elderly, atrial fibrillation, heart disease, diabetes, stroke, high blood pressure	<i>1<sup>st</sup> injection (&lt;1 hour)</i> Tongue oedema with dysphonia, diffuse urticaria	Grade II	Intravenous antihistamines	None	None
<b>Case 4</b>	39	Male	Atopic dermatitis, adrenal insufficiency, alcoholic cirrhosis, osteoporosis	<i>11<sup>th</sup> injection (&lt;1 hour)</i> dizziness, nausea, asthenia, low blood pressure	Grade II	Not detailed	Pfizer-BioNTech mRNA-vaccine (Comirnaty® containing PEG), 3 doses : no reaction.	None
<b>Case 5</b>	34	Female	Asthma, immune thrombocytopenic purpura, Raynaud's phenomenon	<i>1<sup>st</sup> injection (5 minutes)</i> Diffuse urticaria, dizziness, tachycardia, asthma, and hand paresthesia	Grade III	Intramuscular epinephrine, inhaled beta-2 agonists, intravenous corticosteroids	SARS- CoV-2 Pfizer-BioNTech mRNA-vaccine (Comirnaty®), 2 doses: no reaction.	- SPT with PEG (Comirnaty vaccine) and PS80 (pure) : negative.  - No reaction to Xolair introduction (containing PS80).



Accepted manuscript