

DR BASILE CHRÉTIEN (Orcid ID : 0000-0002-7483-2489)

Article type : Research Letter

Dupilumab-associated arthralgia: an observational retrospective study in VigiBase®

Dear Editor, Dupilumab is a human monoclonal antibody that blocks the shared receptor unit for interleukin (IL)-4 and IL-13, and is approved in several indications, including moderate-to-severe atopic dermatitis (AD). According to a recent meta-analysis dupilumab treatment versus placebo resulted in a significant increase in the number of patients who achieved Eczema Area and Severity Index-75 (Rate-Ratio 3.09; 95% CI 2.45-3.89) in different ethnical populations¹.

However, arthralgia and polyarthralgia have recently been reported in dupilumab-treated patients²⁻⁴. In a recent observational cohort study including 100 atopic dermatitis patients treated with dupilumab, 6 patients were diagnosed with enthesitis and/or inflammatory arthropathy⁵. Thus, the aim of the present study was to evaluate the association between arthralgia, enthesopathy and dupilumab exposure using the World Health Organization (WHO) pharmacovigilance database VigiBase®.

Association between dupilumab and these symptoms was assessed using the information component (IC), a Bayesian indicator value of disproportionate reporting in a de-duplicated dataset of VigiBase®. Significance was a lower end of the IC's 95% credibility interval ($IC_{0.025}$) >0. For each report, age, sex, and time to onset were collected. Arthralgia and enthesopathy reports were defined with the Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA, version 22.1) "arthralgia", "enthesopathy", "joint stiffness", and "joint swelling". The data extraction was performed on August 5th, 2020.

Among the 22,341,052 reports in VigiBase®, dupilumab was suspected to be the cause of adverse effects in 28,356 (0.13%) reports. Dupilumab was suspected to be the cause of arthralgia, enthesopathy, joint stiffness and joint swelling in respectively 852 (3.00%), 9 (0.03%), 51 (0.18%) and 137 (0.48%) reports. Dupilumab was associated with a significantly higher reporting of arthralgia, enthesopathy, joint stiffness and joint swelling compared to other medicines in

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJD.20138](#)

This article is protected by copyright. All rights reserved

VigiBase® (Table 1). The median patient age at the time of symptoms onset ranged from 48 to 57 years. Women were overrepresented in arthralgia, joint stiffness and joint swelling with a sex-ratio ranging from 0.32 to 0.62 and men were slightly more represented in enthesopathy with a sex-ratio of 1.25, but the difference was not statistically significant. The median time to onset of arthralgia, joint stiffness and joint swelling ranged from 31 to 76 days after drug initiation and did not statistically differ between the different adverse effects studied.

In our study performed under real-life conditions, we found a significant association between arthralgia, enthesopathy and dupilumab. The sex-ratio between arthralgia, joint stiffness and joint swelling was consistent with a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population (0.60)⁶. However, in a real-life study in an US adult population, women only represented 50.7% of the dupilumab-treated patients⁷. Thus, it's difficult to rule out an effect of sex as a risk factor of dupilumab-induced arthralgia. The time to onset of arthralgia and enthesopathy found in our study was consistent with data from the literature²⁻⁴.

Arthralgia and enthesopathy generally occur during the first few months following the first administration of dupilumab. Willsmore et al. hypothesized that in certain highly atopic individuals, dupilumab, by inhibiting IL-4 and IL-13 signaling, may enhance an IL-17 cell-mediated peripheral spondyloarthritis/psoriatic arthritis pattern of inflammatory arthritis/enthesitis². In an in vitro study on enthesal cells, both IL-4 and IL-13 attenuated lipopolysaccharide-induced enthesal IL-23 production and IL-4 also downregulated secretion of TNF/IL-17A-induced CCL20 from enthesal fibroblasts⁸. These findings suggest a protective role for IL-4/IL-13 in enthesal induction of the IL-23–IL-17 axis and thus strengthen the hypothesis of Willsmore et al. Furthermore T helper 17 cells and associated IL-17, IL-23 have been implicated as key inflammatory mediators in psoriasis. As cases of dupilumab-induced psoriasis have been recently reported, this is another argument in favour of this hypothesis⁵.

De Wijs et al. hypothesized that dupilumab could decrease IL-4 levels, which could potentially cause an increase in TNF α and IL-6 and promote the onset of arthritis³.

Our study was limited by missing information due to the use of a pharmacovigilance database, and the causal relationship between dupilumab and the adverse effect was not always proved.

However, this study highlighted a significant safety signal between dupilumab and arthralgia.

Arthralgia associated with dupilumab may generally occur during the first few months following the first administration. Enthesopathy might be involved. More work is required to define the

exact phenotype and natural history of the presentation. The underlying mechanism is still poorly understood but could imply an enhancement of IL-23 and IL-17 cell-mediated enthesal inflammation. In daily practice, we believe symptoms of arthralgia must be tracked with systematic in-depth patient interview in dupilumab-treated patients.

B. Chrétien,¹ C. Dolladille,¹ J. Alexandre,¹ S. Fedrizzi,¹ V. Lelong-Boulouard,¹ J.C. Lambert² and E. Ezine³

¹Department of Pharmacology, Caen University Hospital, Caen, F-14000, France

²Department of Rheumatology, Saint-Lô Hospital, Saint-Lô, F-50000, France

³Department of Dermatology, Caen University Hospital, Caen, F-14000, France

Correspondence: Basile Chrétien

Email: chretien-b@chu-caen.fr

ORCID: <https://orcid.org/0000-0002-7483-2489>

References

- 1 Agache I, Song Y, Posso M, *et al.* Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: A systematic review for the EAACI biologicals guidelines. *Allergy* 2021; **76**:45–58.
- 2 Willsmore ZN, Woolf RT, Hughes C, *et al.* Development of inflammatory arthritis and enthesitis in patients on dupilumab: a case series. *Br J Dermatol* 2019; **181**:1068–70.
- 3 de Wijs LEM, van der Waa JD, de Jong PHP, Hijnen DJ. Acute arthritis and arthralgia as an adverse drug reaction to dupilumab. *Clin Exp Dermatol* 2020; **45**:262–3.
- 4 Hooper J, Weeks B, Dreyfus DH. Safety And Efficacy Of Dupilumab In Adult Patients With A History Of Eczema Herpeticum. *Journal of Allergy and Clinical Immunology* 2018; **141**:AB230.
- 5 Sears AV, Woolf RT, Gribaleva E, *et al.* Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: a single-centre, prospective 1-year observational cohort study of the first 100 patients treated. *British Journal of Dermatology*; **n/a**. doi:<https://doi.org/10.1111/bjd.19631>.
- 6 Chiesa Fuxench ZC, Block JK, Boguniewicz M, *et al.* Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. *Journal of Investigative Dermatology* 2019; **139**:583–90.

7 Silverberg JI, Guttman-Yassky E, Gadkari A, *et al.* Real-world persistence with dupilumab among adults with atopic dermatitis. *Annals of Allergy, Asthma & Immunology* 2020; **0**. doi:10.1016/j.anai.2020.07.026.

8 Bridegwood C, Sharif K, Freeston J, *et al.* Regulation of enthesal IL-23 expression by IL-4 and IL-13 as an explanation for arthropathy development under dupilumab therapy. *Rheumatology (Oxford)* 2020. doi:10.1093/rheumatology/keaa568.

Funding sources: none.

Conflicts of interest: none to declare.

Table 1. Dupilumab associated arthralgia and enthesopathy: data from VigiBase®

Adverse effects		Arthralgia	Enthesopathy	Joint stiffness	Joint swelling
N		852	9	51	137
IC ₀₂₅		0.9	2.1	0.6	0.6
Age	N available	577	9	38	102
	Median age in years (IQR)	54 (18)	48 (15)	53 (16,5)	57 (16,5)
	p-value	REF	0.61	0.97	0.01
Sex	N available	799	9	49	132
	Sex-ratio	0.62	1.25	0.32	0.61
	p-value	REF	0.32	0.07	0.92
Time to onset	N available	26	3	3	5
	Median time to onset in days (IQR)	30.5 (57.75)	76 (117.5)	36 (20.5)	31 (37)
	p-value	REF	0.38	0.74	0.83
IC: Information Component (a positive IC ₀₂₅ is deemed significant), N: Number of reports, , IQR : Inter-Quartile-Range, REF : reference, Total de-duplicated reports in VigiBase® : 22,341,052 ; Total de-duplicated reports of suspicion of Dupilumab-induced adverse effects in VigiBase®: 28,356					