Original Article

DOI: 10.5582/irdr.2026.01017

Cutaneous lymphomas reported following the use of dupilumab, nemolizumab, tralokinumab, or lebrikizumab: A case investigation based on JADER database and disproportionality analysis

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SUMMARY: Reports of cutaneous lymphomas (CL) following dupilumab administration are increasingly being documented, most frequently in patients with atopic dermatitis (AD). However, information regarding the association between CL and other biologic agents (nemolizumab, tralokinumab, or lebrikizumab) used for the treatment of AD is limited. To date, no large-scale pharmacovigilance study has systematically evaluated this issue in Japan. Therefore, we conducted a case investigation and disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database. Reports registered between April 2004 and August 2025 were analyzed. Both frequentist and Bayesian disproportionality analyses were performed using the reporting odds ratio (ROR) and information component (IC). In the primary analysis, including all reports in the JADER database, the ROR for dupilumab was 257.64 (95% confidence interval [CI], 164.50–404.39), and the IC was 4.52 (IC_{025} = 3.89). For nemolizumab, the ROR was 169.13 (95% CI, 61.78–463.00), and the IC was 2.29 (IC_{025} = 0.95). Reports of CL following tralokinumab or lebrikizumab administration were rare (one and zero cases, respectively) and did not meet the criteria for ROR calculation due to the small number. For sensitivity analysis, disproportionality analyses were restricted to reports with available data on age and sex, submitted by physicians, and cases involving no other suspected drugs. Under these conditions, safety signals based on both the ROR and IC were detected only for dupilumab. The safety signals identified in this study are exploratory in nature and require confirmation in future epidemiological studies.

Keywords: atopic dermatitis, pharmacovigilance, biologic agents, cutaneous T-cell lymphoma, safety signal

1. Introduction

Atopic dermatitis (AD), a chronic inflammatory skin disease, is characterized by pruritic eczematous lesions with a relapsing–remitting course encountered frequently in routine clinical practice (*1*).

Dupilumab was the first biologic agent approved for the treatment of moderate-to-severe AD by the U.S. Food and Drug Administration (FDA) in 2017. It exerts its therapeutic effect by binding to the interleukin-4 receptor alpha (IL-4Rα), thereby inhibiting the signaling pathways of interleukin-4 (IL-4) and interleukin-13 (IL-13) (*2*).

Cutaneous lymphomas (CL) comprise a rare group of malignancies, with an incidence of 0.64 per 100,000 person-years reported in studies from the U.S., with documented racial differences in incidence (*3*). Although the precise incidence in Japan remains unknown, estimates based on a nationwide survey of CL cases conducted by the Prognosis Statistics Committee of the Japanese Skin Cancer Society suggest an incidence of more than 0.4 per 100,000 person-years (*4*).

In recent years, cases of CL diagnosis or worsening following the initiation of dupilumab therapy, particularly among patients treated for AD, are on the rise. Analyses of the FDA Adverse Event Reporting System (FAERS) have identified safety signals for cutaneous T-cell lymphoma (CTCL) associated with dupilumab use (*5,6*). A report suggests that AD itself may be a risk factor for the development of CTCL (*7*).

Nevertheless, information regarding the association between CL and other biologic agents used for the treatment of AD, including nemolizumab, tralokinumab, and lebrikizumab, remains limited (*8,9*). Moreover, to date, no large-scale pharmacovigilance studies have systematically evaluated this issue in Japan. Nemolizumab is an anti–interleukin-31 receptor A (anti–IL-31RA) antibody first approved and launched in Japan in August 2022, and analysis of data in the Japanese Adverse Drug Event Report (JADER) database may therefore provide novel insights into the safety profile of this agent as well as other biologics used for the

treatment of AD.

Therefore, in this study, we conducted a case investigation and disproportionality analysis using the JADER database to evaluate the association between biologic agents for AD and CL.

2. Materials and Methods

2.1. Data source

Data registered in the JADER database between April 2004 and August 2025 were obtained from the official website of the Pharmaceuticals and Medical Devices Agency (PMDA) (*http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp*). The JADER database consists of four datasets: patient demographic information (demo), drug information (drug), adverse event information (reac), and medical history information (hist).

In this study, four biologic agents approved for the treatment of AD, namely dupilumab, nemolizumab, tralokinumab, and lebrikizumab, were selected as the target drugs. Adverse events recorded in the "reac" dataset are coded using Preferred Terms (PTs) based on the Medical Dictionary for Regulatory Activities, Japanese version (MedDRA/J).

Adverse events related to CL were defined according to previously published pharmacovigilance studies (*10*), with minor modifications to incorporate clinically relevant MedDRA/J PTs applicable to the present study. Specifically, the following PTs listed in MedDRA/J version 28.1J were included and defined as CL: "Cutaneous lymphoma (PT code: 10079945)", "Cutaneous T-cell lymphoma (PT code: 10011677)", "Cutaneous T-cell lymphoma stage I (PT code: 10011680)", "Cutaneous T-cell lymphoma stage II (PT code: 10011681)", "Cutaneous T-cell lymphoma stage III (PT code: 10011682)", "Cutaneous T-cell lymphoma stage IV (PT code: 10011683)", "Cutaneous T-cell lymphoma refractory (PT code: 10011679)", "Cutaneous T-cell lymphoma recurrent (PT code: 10011678)", and "Cutaneous B-cell lymphoma (PT code: 10085518)".

From all cases registered in the JADER database, those where both the target drugs and the predefined adverse events were recorded were extracted as a "case investigation". The following variables were analyzed: sex, age, drug involvement, indications, reporter of the adverse event, and clinical outcomes. In the JADER database, patient age is generally recorded in 10-year intervals (*e.g.*, 10s, 20s, 30s); however, in some cases, age is recorded using specific categories such as "neonate", "infant", "child", "adolescent", "adult", or "elderly".

Indications were classified as AD or others; when multiple indications were reported, cases were classified as AD if this condition was among the reported indications. Adverse event reporters were categorized as physicians or others; when multiple reporters were listed, reports were categorized as physician-reported if a physician was among the reporters. Drug involvement was categorized as suspected drugs, drug interactions, or concomitant drugs. In this study, only cases where the target drugs were reported as suspected drugs were included in the analysis. Cases involving multiple suspected drugs were included in the primary analysis for each reported suspected drug but were excluded from the sensitivity analysis. Clinical outcomes of CL cases were classified as poor, when defined as unrecovered, death, or with sequelae, or classified as favorable, when defined as recovery or in remission. Lacking data were categorized as "Missing or Unknown".

2.2. Statistical analysis

Descriptive statistics were used to summarize the results. Disproportionality analysis was conducted to evaluate the association between drugs and adverse events. In accordance with previous reports, both frequentist and Bayesian disproportionality analyses were performed using the reporting odds ratio (ROR) and the information component (IC), respectively (*11*). A positive signal was defined as a lower limit of the 95% confidence interval (CI) of the ROR greater than 1 and a lower limit of the 95% CI of the IC (IC_{025}) greater than 0. A sensitivity analysis was performed using a restricted dataset comprising physician-reported cases with complete data on sex and age, and without concomitant suspected drugs to evaluate the robustness of the disproportionality analysis under more stringent reporting conditions while minimizing potential information bias, reporter bias, and confounding from concomitant suspected drugs. All data were analyzed using EZR ver. 1.70 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (*12*).

2.3. Ethical considerations

This study adhered to the principles outlined in the Declaration of Helsinki and complied with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The analysis was based exclusively on secondary use of publicly accessible data and did not require direct interaction with, or intervention in, human participants. Accordingly, formal ethical review and approval were waived by the institutional ethics committee. All data obtained from the JADER database were anonymized by the responsible regulatory authorities before being made available for research purposes.

3. Results

The JADER database used in this study comprised a total of 1,002,922 cases. Among these, dupilumab, nemolizumab, tralokinumab, and lebrikizumab were

registered as suspected drugs in 1,196, 232, 18, and 11 cases, respectively. In addition, 108 cases reported CL as an adverse event. The time trend of reports related to CL is shown in Figure 1A.

Among the 108 cases in which CL was reported, dupilumab was the most frequently reported suspected drug, accounting for 25 cases (23.1%) (Figure 1B). Nemolizumab use was associated with four cases, and tralokinumab use with one case; however, the case associated with tralokinumab use was the same as one of the cases associated with nemolizumab use, indicating that two suspected drugs were reported in a single case. No case of lebrikizumab use in association with CL was identified.

Because dupilumab is approved for multiple indications, we examined the indications for which it was prescribed. Among the 1,196 cases in which dupilumab was registered as a suspected drug, 522 cases (43.6%) were treated for AD (Figure 1C). Amid these 522 cases, 19 (3.6%) were associated with reports of CL (Figure 1D).

The characteristics of the 25 cases where CL was reported following dupilumab administration—including sex, age, indication, reporter of the adverse event, the presence or absence of other suspected drugs, and clinical outcomes—are summarized in a Sankey plot (Figure 1E). In one case, another suspected drug, upadacitinib hydrate, was also reported.

In the primary disproportionality analysis using all reports in the JADER database, dupilumab showed an

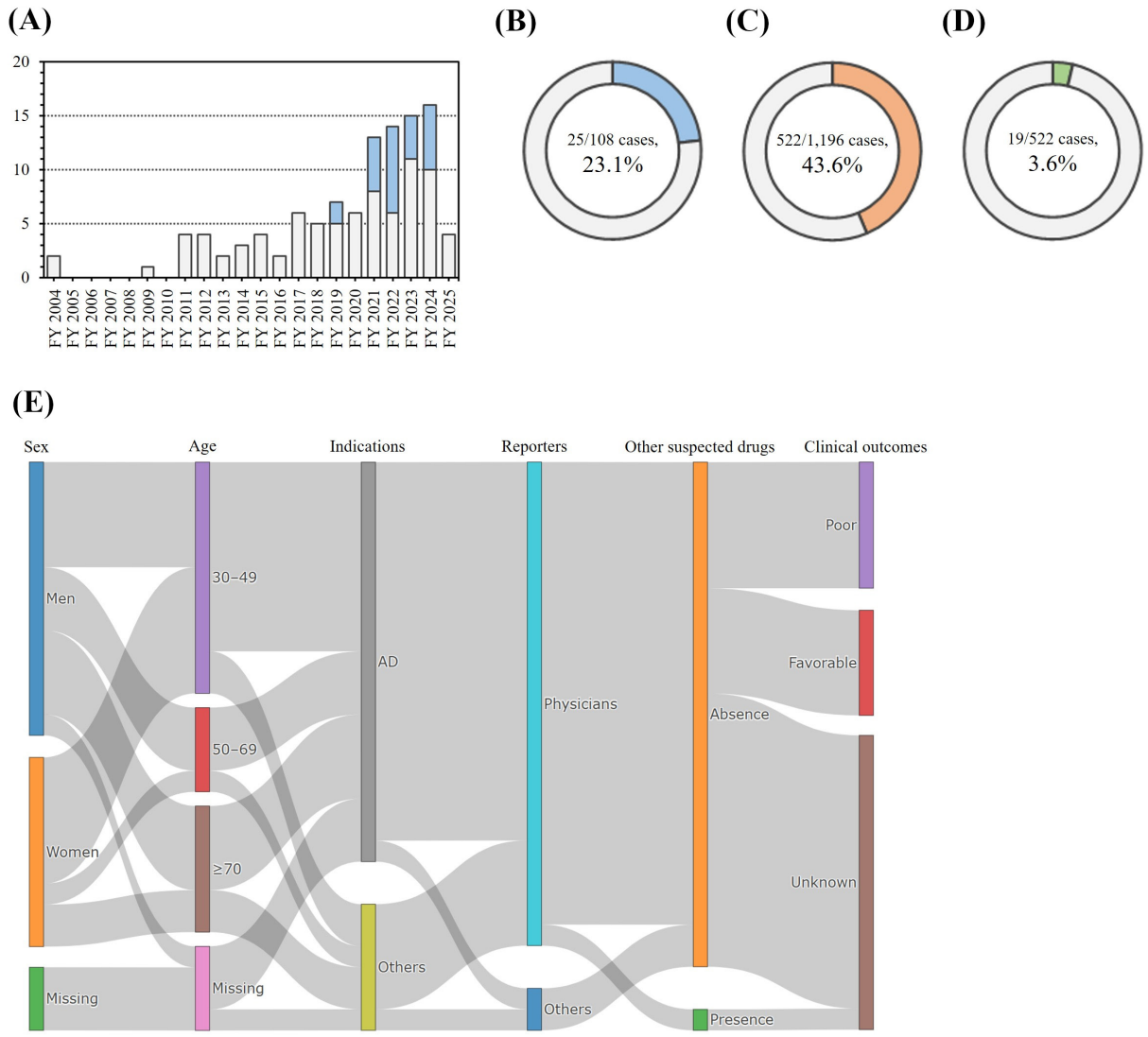

Figure 1. Characteristics of cutaneous lymphoma cases associated with dupilumab use. Panel **(A)** shows the time trend of reports related to cutaneous lymphoma; reports associated with dupilumab use are shown in blue. Panel **(B)** shows the number and proportion of cases in which dupilumab use was reported as a suspected drug among the 108 cutaneous lymphoma cases. Panel **(C)** shows the number and proportion of cases with atopic dermatitis as the indication among those in which dupilumab use was reported as a suspected drug. Panel **(D)** shows the number and proportion of cases in which cutaneous lymphoma was reported among patients treated with dupilumab for atopic dermatitis. Panel **(E)** presents a Sankey plot summarizing the characteristics of the 25 cases where cutaneous lymphoma was reported after dupilumab treatment, including sex, age, indication, reporter type, presence of other suspected drugs, and clinical outcomes.

ROR of 257.64 (95% CI, 164.50–404.39) and an IC of 4.52 (IC_{025}=3.89). Nemolizumab demonstrated an ROR of 169.13 (95% CI, 61.78–463.00) and an IC of 2.29 (IC_{025}=0.95). In contrast, CL was rare following administration of tralokinumab or lebrikizumab (1 and 0 cases, respectively), and the number of reports was insufficient to meet the criteria for calculation of ROR or meaningful IC estimation (Table 1).

As a sensitivity analysis, disproportionality analysis was restricted to reports with available data on age and sex, submitted by physicians, and without concomitant suspected drugs. Under these conditions, 19 of the 25 dupilumab-associated CL reports and 2 of the 4 nemolizumab-associated CL reports remained eligible for analysis. A safety signal based on both the ROR and IC was detected only for dupilumab. Although an ROR-based signal was also observed for nemolizumab, the IC signal was attenuated and no longer met the predefined criteria for signal detection (Table 2).

4. Discussion

This study conducted a case investigation and disproportionality analyses of reports of CL following treatment with four biologic agents approved for AD.

Dupilumab was the most frequently reported suspected drug associated with CL, accounting for 25 cases. Four cases were reported in association with nemolizumab use, and one case with tralokinumab use; however, one of the nemolizumab-associated cases overlapped with the single tralokinumab-associated case, indicating that two suspected drugs were reported in a single case. In contrast, no cases of CL were reported in association with lebrikizumab use. Because dupilumab is approved for multiple indications in addition to AD, including asthma and chronic rhinosinusitis with nasal polyps, interpretation of the observed signal requires consideration of the treated population. In the present study, 19 of the 25 reported CL cases associated with dupilumab occurred in patients treated for AD, whereas no cases were reported in patients treated for asthma or chronic rhinosinusitis with nasal polyps. Several reports included other recorded indications that were not listed as approved indications in the package insert, such as eosinophilic gastrointestinal disorders, CTCL, or rash. These findings suggest that the observed signal was primarily driven by reports from the AD population, although indication data were unavailable or heterogeneous in a subset of cases. Furthermore, a literature search in PubMed and Ichushi-Web, as of February 5, 2026, identified seven case reports from Japan in which CL developed or became clinically apparent following dupilumab treatment (*13-19*). Although the JADER database does not provide detailed clinical information comparable to those available in published case reports, the inclusion of 25 cases in the analysis is considered informative as real-world pharmacovigilance data from Japan. Identification of four cases following nemolizumab treatment warrants attention.

In the primary analysis, including all available reports, safety signals for CL were detected for dupilumab and nemolizumab based on both ROR and IC. In contrast, reports of CL following tralokinumab or lebrikizumab treatment were limited (one and zero cases, respectively), and the number of reports was insufficient to meet the minimum criteria required for ROR calculation. In addition, dupilumab was approved earlier and has been more widely used in clinical practice in Japan than several other biologic agents included in this study. Therefore, the larger number of reports associated with dupilumab may partly reflect longer post-marketing exposure, greater cumulative patient exposure, and increased clinical awareness

Table 1. Disproportionality analysis for all available data

	Case	Non-case	ROR (95% CI)	IC (IC_{025})
Dupilumab	25	1,171	257.64 (164.15–404.39)	4.52 (3.89)
Nemolizumab	4	288	169.13 (61.78–463.00)	2.29 (0.95)
Tralokinumab	1	17	NA	NA
lebrikizumab	0	11	NA	NA

Notes: NA, not applicable due to an insufficient number of reports. *Abbreviations*: ROR, reporting odds ratio; IC, information component; 95% CI, 95% confidence interval; IC_{025}, lower limit of 95% confidence interval of CI.

Table 2. Sensitivity analysis for physician-reported cases with complete sex and age data and without other suspected drugs

	Case	Non-case	ROR (95% CI)	IC (IC_{025})
Dupilumab	19	699	299.41 (178.47–502.32)	4.20 (3.48)
Nemolizumab	2	213	81.78 (19.98–334.74)	1.55 (–0.16)

Abbreviations: ROR, reporting odds ratio; IC, information component; 95% CI, 95% confidence interval; IC_{025}, lower limit of 95% confidence interval of CI.

rather than differences in the underlying risk of CL. Differences in reporting dynamics related to approval timing and market penetration, including potential Weber effect-related influences (*20*), should therefore be considered when interpreting disproportionality signals across agents. As a sensitivity analysis, a disproportionality analysis was restricted to reports with available age and sex information, submitted by physicians, and without concomitant suspected drugs. Under these more stringent conditions, safety signals for dupilumab were consistently detected using both the ROR and IC, suggesting a degree of internal consistency across different analytical conditions. Although the ROR-based signal for nemolizumab persisted, the IC-based signal was no longer observed, indicating uncertainty regarding the stability and robustness of this signal across analytical assumptions. Differences in the pharmacological mechanisms of these agents may provide contextual information for interpreting these findings. Furthermore, time-to-onset (TTO) analysis was not performed because only a limited number of reports contained sufficiently complete temporal information. In addition, for diseases such as CL, the reported adverse event onset date may reflect the timing of diagnosis rather than the actual biological onset of disease, thereby limiting the interpretability of TTO analyses based on spontaneous reporting data.

Dupilumab targets the IL-4Rα and inhibits IL-4 and IL-13 signaling, whereas tralokinumab and lebrikizumab selectively block IL-13, resulting in a more skin-focused modulation of type 2 inflammation. IL-4 plays a central role in the initiation and amplification of type 2 immune responses by promoting Th2 differentiation and IgE class switching, while IL-13 is more prominently involved in downstream tissue inflammation and epidermal barrier dysfunction (*21*). Both IL-4 and IL-13 have been implicated in the formation of a Th2-dominant, tumor-supportive tumor microenvironment in CTCL (*22,23*). However, whether blockade of these cytokines directly promotes lymphoma development or progression is unclear (*24*). Many reported cases of CTCL following dupilumab treatment have been interpreted as the unmasking or clinical manifestation of pre-existing subclinical disease rather than de novo tumor induction, and findings of this study are consistent with this interpretation (*25,26*). In addition, early-stage CTCL may clinically resemble AD and therefore initially be misdiagnosed prior to initiation of biologic treatment. Consequently, confounding by indication and diagnostic uncertainty may have contributed to the observed reporting signals. Similarly, fewer CTCL reports associated with IL-13–targeting antibodies such as tralokinumab and lebrikizumab should not be interpreted as evidence of absence of risk, particularly given the limited post-marketing exposure in Japan. Accordingly, the apparent scarcity of reports for these agents should be interpreted cautiously and does not preclude the possibility of rare or delayed adverse events becoming evident with longer-term or broader clinical use.

IL-31 is a cytokine involved in Th2 inflammation and the neuroimmune axis, and expression of the IL-31 receptor (IL-31RA/OSMRβ) has been observed in CTCL lesions (*27*). However, previous studies have not demonstrated a consistent association between IL-31 levels or receptor expression and CTCL disease severity or progression (*28,29*). This suggests that IL-31/IL-31RA signaling may primarily reflect the inflammatory and pruritic immune microenvironment rather than tumor biology itself. The safety signal detected for nemolizumab may represent one aspect of CTCL-associated immune responses; however, evidence for a direct tumor-promoting effect remains limited at present (*30*). Nevertheless, further studies are needed to evaluate long-term safety.

This study has several limitations inherent to spontaneous reporting databases. First, disproportionality measures such as the ROR and IC reflect reporting imbalances within a spontaneous reporting database rather than true incidence or relative risk, and therefore do not establish causality. As with all pharmacovigilance studies based on spontaneous adverse event reports, the findings reflect reported events rather than true incidence and may be influenced by time-dependent reporting dynamics, differences in market duration, and reporting awareness, including the Weber effect (*20*). Under-reporting and selective reporting could also have affected reporting patterns over time; therefore, the true incidence of CL could not be estimated from the JADER database. Second, channeling bias could not be fully excluded, as certain biologic agents may be preferentially prescribed to patients with more severe or long-standing AD, who may differ systematically from patients receiving other treatments. However, because detailed information regarding AD severity was not available in the JADER database, the potential influence of disease severity on treatment selection and baseline CTCL risk could not be directly evaluated. Third, confounding by indication was a concern, as AD itself, particularly in severe cases, may be associated with an increased risk of CTCL (*7*). In addition, early-stage CTCL may clinically mimic AD and remain unrecognized prior to initiation of biologic treatment, raising the possibility that some reported cases represented the unmasking of pre-existing disease rather than treatment-induced lymphoma. Fourth, because the JADER database is based on spontaneous adverse event reporting, duplicate reports and follow-up reports referring to the same case may have been included. Although potential duplicate cases can be partially identified using demographic and temporal information, complete and reliable duplicate removal was not feasible in the present study because of a substantial amount of missing data. Therefore, the possibility of residual

duplicate reports could not be excluded. Overall, the observed safety signals should be interpreted with caution and should not be regarded as evidence of a causal relationship.

In conclusion, safety signals identified in this study should be considered exploratory, and further epidemiological and clinical studies are required to more clearly evaluate these associations.

Funding: None.

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

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Received February 20, 2026; Revised May 14, 2026; Accepted June 16, 2026.

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Released online in J-STAGE as advance publication July 8, 2026.