Does dupilumab increase lymphoma risk in eczema patients?

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Atopic dermatitis, commonly known as eczema, is a chronic inflammatory skin condition affecting millions, often profoundly impacting quality of life. For patients with moderate-to-severe disease, systemic therapies are often necessary, but these carry their own set of concerns, particularly regarding long-term safety.
The advent of targeted biologics like dupilumab has transformed management, offering significant relief for many. But with any immunomodulatory agent, clinicians must consider the potential for rare, serious adverse events, including malignancy. The question of a link between dupilumab and lymphoma in eczema patients has therefore been a persistent, if largely unsubstantiated, concern.

KEY TAKEAWAYS

- The Pivot: Despite initial concerns, large-scale real-world data and clinical trial analyses have not established a causal link between dupilumab and increased lymphoma risk.
- The Data: The observed incidence of lymphoma in dupilumab-treated patients aligns with or is lower than that seen in the general atopic dermatitis population and the general population.
- The Action: Clinicians should continue to monitor patients for malignancy according to standard practice, recognising that atopic dermatitis itself may carry a slightly elevated lymphoma risk.

Atopic dermatitis is a complex, chronic inflammatory skin disease driven by type 2 inflammation, characterised by intense pruritus, eczematous lesions, and a significant burden on patients' daily lives. The condition is associated with dysregulation of the immune system, specifically an overexpression of interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. These cytokines are central to the pathogenesis of atopic dermatitis, promoting IgE production, eosinophil activation, and barrier dysfunction. Historically, treatment for moderate-to-severe atopic dermatitis relied on broad immunosuppressants, which carried considerable risks of infection and other systemic side effects. The need for more targeted, safer therapies was clear.
Dupilumab, a fully human monoclonal antibody, specifically targets the IL-4 receptor alpha subunit, thereby blocking signalling from both IL-4 and IL-13. This mechanism of action directly addresses the core inflammatory pathways in atopic dermatitis. Approved for moderate-to-severe atopic dermatitis in adults and children, dupilumab has demonstrated impressive efficacy in clinical trials, showing significant improvements in Eczema Area and Severity Index (EASI) scores, pruritus, and quality of life. Its introduction marked a significant advance, offering a more precise immunomodulation compared to older systemic agents. However, as with any therapy that modulates the immune system, particularly one used long-term, vigilance for potential adverse events, including malignancy, is paramount. The question

of whether dupilumab, by altering immune surveillance, could increase the risk of lymphoma has been a recurring point of discussion among clinicians and patients.

Understanding the Baseline Risk of Lymphoma in Eczema

The discussion around dupilumab and lymphoma must begin with the understanding that atopic dermatitis itself is associated with a slightly elevated risk of certain malignancies, particularly lymphomas. This is not unique to atopic dermatitis; chronic inflammatory conditions generally carry an increased risk of lymphoproliferative disorders. The exact mechanisms are not fully elucidated but are thought to involve chronic immune stimulation, dysregulation of immune surveillance, and potentially the effects of long-term systemic immunosuppressive therapies used to manage the condition. For instance, a meta-analysis of observational studies found a small but statistically significant increased risk of lymphoma in patients with atopic dermatitis compared to the general population. This baseline risk complicates the assessment of any new therapy, as an observed lymphoma case in a treated patient might be attributable to the underlying disease rather than the drug.

The chronic inflammation in atopic dermatitis leads to persistent activation and proliferation of immune cells, particularly T cells. This sustained cellular turnover and cytokine milieu could theoretically create an environment more permissive for malignant transformation. Furthermore, some patients with severe atopic dermatitis receive systemic immunosuppressants like cyclosporine or methotrexate, which themselves carry known, albeit small, risks of malignancy. Distinguishing between the disease-associated risk, treatment-associated risk, and any potential drug-specific risk requires careful epidemiological analysis and large patient cohorts.

Clinical Trial Data on Malignancy

The initial safety profile of dupilumab emerged from a comprehensive clinical development program involving thousands of patients across multiple Phase 2 and Phase 3 trials. These trials, including LIBERTY AD SOLO 1, SOLO 2, and CHRONOS, consistently reported malignancy rates that were comparable between dupilumab-treated groups and placebo groups. For example, in the SOLO trials, the incidence of malignancy was low in both arms, with no statistically significant difference observed. The CHRONOS trial, which evaluated dupilumab with topical corticosteroids, similarly found no increased signal for malignancy. These short-term, placebo-controlled trials provided the first reassurance, but their duration was inherently limited, making it difficult to detect rare, long-latency events like lymphoma.

Long-term extension studies, such as LIBERTY AD OLE, have provided more extensive follow-up data, accumulating patient-years of exposure to dupilumab. These studies, which can extend for several years, continue to monitor for adverse events, including malignancies. The cumulative data from these long-term extensions has consistently shown that the overall incidence of malignancies, including lymphomas, in dupilumab-treated patients remains consistent with what would be expected in the general atopic dermatitis population. No new or unexpected malignancy signals have emerged from these extended observation periods. This sustained lack of signal across thousands of patient-years of exposure is a critical piece of evidence.

Real-World Evidence and Post-Marketing Surveillance

Beyond controlled clinical trials, real-world evidence and post-marketing surveillance provide invaluable insights into drug safety in broader, more diverse patient populations. Regulatory agencies worldwide, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), continuously collect and analyse adverse

event reports for approved medications. For dupilumab, these extensive databases have not identified an increased risk of lymphoma. The observed rates of lymphoma in patients receiving dupilumab in routine clinical practice have not exceeded the background rates seen in patients with atopic dermatitis or the general population.

Several large observational studies and registry analyses have further corroborated these findings. For instance, studies utilising large insurance claims databases or national health registries have compared malignancy rates in dupilumab users versus those on other systemic treatments or no systemic treatment. These studies have generally concluded that dupilumab does not appear to increase the risk of lymphoma. Some analyses have even suggested a numerically lower incidence of malignancy in dupilumab-treated patients compared to those on conventional immunosuppressants, though these comparisons are often confounded by differences in patient characteristics and duration of follow-up. The Oxford Handbook of Clinical Haematology provides a comprehensive overview of lymphoproliferative disorders, which can be a useful reference for clinicians.

Mechanistic Considerations

From a mechanistic perspective, dupilumab's targeted action on IL-4/IL-13 signalling does not inherently suggest a pro-lymphomagenic effect. IL-4 and IL-13 are primarily involved in type 2 immune responses, allergic inflammation, and tissue remodelling. While these cytokines can influence B cell activation and antibody production, their direct role in promoting lymphomagenesis is not as clearly established as, for example, the role of Epstein-Barr virus (EBV) in certain lymphomas or the broad immunosuppression seen with calcineurin inhibitors. Dupilumab's mechanism is distinct from therapies that broadly suppress T-cell function or those that target TNF-alpha, which have different safety profiles regarding malignancy.

The immune system's role in tumour surveillance is complex. While some broad immunosuppressants can impair this surveillance, leading to an increased risk of malignancy, dupilumab's more specific modulation of type 2 immunity does not appear to have this effect. It is plausible that by reducing chronic inflammation and immune dysregulation associated with severe atopic dermatitis, dupilumab might even indirectly mitigate some of the disease-associated malignancy risk, although this remains a hypothesis requiring further investigation. The current understanding of IL-4 and IL-13 pathways does not point to a direct oncogenic role for dupilumab.

The Catch: Limitations and Ongoing Vigilance

Despite the reassuring data, several caveats warrant consideration. The follow-up duration, while extensive, may still not be long enough to definitively rule out extremely rare, very long-latency malignancies. Lymphomas can take many years to develop, and even large real-world datasets have inherent limitations in capturing every potential risk over decades. Furthermore, while the overall incidence of lymphoma has not increased, it is always challenging to detect signals for very rare subtypes of lymphoma or in specific, small subgroups of patients. The general atopic dermatitis population itself is heterogeneous, and certain patient characteristics, such as severe disease duration or prior exposure to multiple systemic immunosuppressants, might influence individual risk profiles.

The open-label nature of many long-term extension studies and real-world observational studies means they are susceptible to confounding factors and reporting biases. While statistical methods attempt to adjust for these, they can never fully replicate the rigour of a double-blind, placebo-controlled trial. Clinicians must also remember that patients with atopic dermatitis may present with lymphadenopathy as part of their inflammatory disease, which can sometimes be

mistaken for lymphoma. Careful clinical assessment and, when indicated, biopsy, remain essential for accurate diagnosis. The Oxford Handbook of Medical Dermatology offers guidance on distinguishing inflammatory lymphadenopathy from malignant causes.

Ultimately, the current body of evidence, encompassing both controlled clinical trials and extensive real-world data, provides strong reassurance that dupilumab does not increase the risk of lymphoma in patients with atopic dermatitis. The observed rates of lymphoma are consistent with or lower than the background rates in the atopic dermatitis population and the general population. This allows clinicians to prescribe dupilumab with confidence regarding this specific malignancy risk. Ongoing pharmacovigilance remains critical, as it does for all long-term therapies. Future research will continue to refine our understanding of long-term safety, particularly in specific patient subgroups and over even longer durations of exposure.

CLINICAL IMPLICATIONS

The persistent concern regarding dupilumab and lymphoma risk, while understandable given its immunomodulatory nature, appears largely unfounded by the current evidence. Clinicians can largely put this specific worry aside when considering dupilumab for appropriate patients with moderate-to-severe atopic dermatitis. The data consistently points to no increased risk beyond the baseline associated with atopic dermatitis itself.

This clarity allows for more confident prescribing decisions, particularly for patients who have exhausted topical options or failed conventional systemic immunosuppressants. The focus should remain on the significant efficacy benefits dupilumab offers in controlling severe eczema symptoms and improving quality of life, rather than an unsubstantiated malignancy signal.

But this does not negate the need for ongoing clinical vigilance. Patients with chronic inflammatory conditions, including atopic dermatitis, inherently carry a slightly higher risk of certain malignancies. Regular skin checks, lymph node examinations, and appropriate screening for age and risk factors should continue as standard practice, irrespective of dupilumab use. Any new or persistent lymphadenopathy still warrants thorough investigation.

The broader implication is that targeted biologics, by specifically modulating inflammatory pathways rather than broadly suppressing the immune system, may offer a more favourable long-term safety profile regarding malignancy compared to older, less specific immunosuppressants. This distinction is crucial for patient counselling and for shaping future treatment algorithms in dermatology.

REFERENCES

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