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# Dupilumab, Asthma, and Lymphoma — Signal or Surveillance Bias?

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The advent of biologic therapy has transformed the management of severe asthma. Dupilumab, a monoclonal antibody targeting the interleukin (IL)-4 receptor α subunit, inhibits IL-4 and IL-13 signalling pathways, which are central to type 2 inflammation. It is now well established as an effective steroid-sparing therapy, reducing exacerbations and improving lung function by attenuating IgE-mediated pathways, eosinophilic recruitment, goblet cell hyperplasia and mucus production.

In a large US population-based cohort study, Ma and colleagues[1] address an important safety concern: whether Dupilumab increases lymphoma risk among patients with asthma.

The study has several notable methodological strengths including its large sample size, active comparator design using inhaled corticosteroid/long-acting β2-agonist (ICS/LABA) therapy, application of a target trial emulation framework, and rigorous 1:1 propensity score matching, resulting in 14 900 patients per treatment arm. The authors report an association between Dupilumab exposure and an increased risk of new-onset lymphoma, particularly mature T- and NK-cell subtypes.[1] The consistency of the signal for T-cell–predominant lymphomas across multiple analyses, including sensitivity testing, merits careful consideration.

However, several limitations merits cautious interpretation.

First, residual confounding and confounding by indication remain plausible despite matching. Patients selected for Dupilumab typically have a more severe asthma phenotype, characterised by greater healthcare utilisation. Increased clinical surveillance in this population may heighten the likelihood of malignancy detection, introducing potential surveillance bias.

Second, the choice of comparator arm may be suboptimal. Comparing Dupilumab recipients with patients receiving ICS/LABA therapy may not fully account for differences in disease severity. A biologic-to-biologic comparison—particularly with agents not targeting the IL-4/IL-13 pathway—would provide a more appropriate control. Additionally, clarification is needed regarding prior biologic exposure and treatment switching, as previous immunomodulatory therapy could influence malignancy risk.

Third, reliance on ICD-10 diagnostic coding without pathological confirmation limits diagnostic precision. This is particularly relevant for cutaneous T-cell lymphoma, which is well recognised for being misdiagnosed as inflammatory dermatoses in its early stages.[2,3]

Fourth, absolute event numbers were small, with several subtype analyses based on ten or fewer cases and accompanied by wide confidence intervals. These factors raise concerns regarding statistical stability and the potential for overestimation of effect size.

Importantly, the reported reduction in all-cause mortality (hazard ratio 0.65) aligns with findings from pivotal clinical trials demonstrating improved asthma control, reduced systemic corticosteroid exposure, and fewer severe exacerbations [4,5]. This favourable survival signal reinforces the established benefit–risk profile of Dupilumab in severe asthma management. While any potential malignancy signal warrants vigilance, it must be interpreted within the broader clinical context. Long-term extension studies have generally supported a reassuring safety profile in asthma populations.[6]

At present, these findings should prompt clinical vigilance rather than changes in therapy. Appropriate patient counselling regarding rare or uncertain lymphoma risk, alongside continued monitoring for lymphadenopathy, B symptoms, cytopenias, and atypical cutaneous findings, is prudent. Prospective registries, longer-term follow-up, and biologic-to-biologic comparative studies will be essential to determine whether this association reflects causality, underlying disease biology, or a surveillance artefact.

Until further data emerge, Dupilumab remains an effective and potentially life-modifying therapy for appropriately selected patients with severe asthma.

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