NEWS, VIEWS, AND REVIEWS

Connecting the Plaques: Exploring the Link Between Dupilumab and Cutaneous T-cell Lymphoma

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BACKGROUND

Recent literature has suggested a link between dupilumab, a monoclonal antibody targeting receptors for interleukin (IL)-4 and IL-13, and cutaneous T-cell lymphoma (CTCL).[1,2] Approved in 2017 for moderate to severe atopic dermatitis (AD), dupilumab safely and effectively treats AD by blocking IL-4/13 signaling and inhibiting T-helper (Th)-2-mediated pathways.[1,2] Dupilumab is also used to treat asthma, prurigo nodularis, allergic rhinitis, eosinophilic esophagitis, chronic urticaria, and bullous pemphigoid.[3]

An analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database reported a 30.0-fold increased proportional reporting ratio (95% confidence interval (CI) 25.0–35.9) for CTCL in dupilumab users.[4] There are 3 leading theories for this association: 1) CTCL developing as a result of chronic AD, 2) CTCL directly triggered by dupilumab, and 3) CTCL unmasked or accelerated by dupilumab.[1] Although several hypotheses have been proposed, a causal relationship has yet to be established. In this review, we critically evaluate the quality and limitations of the current literature on dupilumab and CTCL.

Theory 1: CTCL Arising from Chronic AD

Chronic AD is a known CTCL risk factor, with both diseases sharing STAT3 and CARD11 gene mutations, as well as Th2-dominated CD4+ lymphocyte inflammation.[5,6] Murine models also suggest that sustained inflammation is required for CTCL lesion development.[5]

Studies have highlighted a potential link between chronic AD and CTCL. Lavin et al reported an odds ratio (OR) of 8.81 for developing CTCL among patients treated with dupilumab for cutaneous indications, while no confirmed CTCL cases were observed in those using dupilumab for non-cutaneous indications.[7] Kook et al also explored chronic AD's potential role in the development of mycosis fungoides (MF), the most common CTCL subtype.[2,6] Among 371 AD patients treated with dupilumab, 46 were classified as poor responders. Of a subset of these patients (n=35), 19 were found to have MF.[6] Notably, 15 patients improved after eight weeks of MF-directed therapy (narrow-band ultraviolet B, methotrexate, or retinoids) while continuing dupilumab.[6] This improvement despite ongoing dupilumab therapy challenges the theory of dupilumab as a direct trigger and instead underscores the potential for CTCL to arise in the setting of chronic AD. However, this study is limited by a small sample size, limited follow-up, and potential AD misdiagnosis due to the lack of pre-dupilumab treatment biopsies, leaving dupilumab's potential role in CTCL progression inconclusive.

Theory 2: Dupilumab as a Direct Trigger of CTCL

Various studies have suggested a direct link between dupilumab use and CTCL. A retrospective cohort study by Liao et al identified 30 CTCL cases following dupilumab exposure.[1] While 22 of 32 patients had prior biopsies confirming AD, the timing relative to dupilumab initiation was unclear, and only 5 underwent re-evaluation before starting treatment, raising uncertainty about pre-existing CTCL.[1] The single-center, retrospective design further limits the ability to conclude a causal relationship. Similarly, Hasan et al, using a TrinetX database review, reported increased odds of CTCL in dupilumab-treated AD patients compared to those not receiving dupilumab or disease-modifying antirheumatic drugs (OR 3.202; 95% CI 1.573–6.514; number needed to harm (NNH): 833), though interpretation is limited by potential database misclassification and lack of disease severity data.[8] While both studies suggest an association, neither provides convincing evidence of causality, and the relatively high NNH diminishes concern regarding dupilumab's safety in this context.

Proposed mechanisms linking dupilumab to CTCL include its potential to induce lymphoid reactions (LR), infiltrates that differ slightly from the histopathologic characteristics of CTCL in the location of epidermal cerebriform lymphocytes.[2] Boesjes et al reported 11 dupilumab-treated patients with atypical infiltrates consistent with MF or LR, hypothesizing that IL-4/13 blockade may trigger benign LRs with potential for malignant transformation via clonal T-cell expansion.[2] Dupilumab may also disrupt the Th1/Th2 balance by shifting immunity toward Th1 pathways. Since early MF is Th1-mediated, this suggests the possibility that dupilumab promotes early CTCL.[2,5] These theories lack long-term outcome data, highlighting the need for further research.

Theory 3: Dupilumab Unmasking or Accelerating CTCL

Several case reports propose that dupilumab may unmask or accelerate the progression of CTCL. A case of primary cutaneous γδ T-cell lymphoma (PCGD-TCL), a rare and aggressive variant of CTCL, was identified in a 62-year-old woman undergoing 18 months of treatment with dupilumab for suspected, non-biopsy confirmed AD that persisted since childhood.[9] While on dupilumab, she developed diffuse cutaneous ulcers and erosions and experienced rapid clinical deterioration; post-mortem evaluation confirmed a diagnosis of PCGD-TCL.[9] This case suggests dupilumab's potential role in unmasking a severe form of CTCL in a patient with years of chronic AD. However, the severity and chronicity of this patient's disease make it difficult to determine whether dupilumab unmasked CTCL or if the exacerbation reflected years of uncontrolled inflammation.

Further, Russomanno et al reported a patient with severe AD without baseline CTCL who was diagnosed with CTCL 2 months after starting dupilumab.[10] The patient had extensive disease and recurrent infections, suggesting chronic AD itself may have elevated CTCL risk. Although a single case report limits generalizability, the rapid onset raises the possibility that dupilumab unmasked preexisting CTCL.[10] Similarly, Hollins et al described three patients with initial biopsies suggesting nonspecific eczematous or psoriasiform dermatitis.[11] Within 6 to 12 weeks of dupilumab initiation, these patients experienced clinical deterioration, and subsequent biopsies revealed CTCL.[11] Hollins et al believe that the nondiagnostic dermatitis evident on the initial biopsies may have reflected early-stage CTCL that progressed following dupilumab initiation.[11] Additionally, the timing of the initial biopsies was not specified, raising further concern for the misdiagnosis of pre-existing CTCL before dupilumab use.

Theories on dupilumab's potential unmasking of CTCL suggest that IL-13Rα1 blockade increases IL-13 availability, potentially activating IL-13Rα2, a receptor not inhibited by dupilumab, and promoting CTCL progression.[5,11] Cabrera-Perez et al identified transcript-level alterations in IL-13 receptor expression in keratinocytes from both AD and CTCL patients, implicating IL-13 as a possible driver of CTCL.[4] Additionally, IL-4 blockade may disrupt the tumor equilibrium phase, when tumor cells remain dormant under immune surveillance, allowing subclinical CTCL to manifest, though this idea remains theoretical and underexplored.[5]

Although anecdotal evidence and proposed mechanisms support this theory, the evidence remains even more limited and largely experimental. The hypotheses put forward by Hollins, Cabrera-Perez, and Guglielmo et al are plausible but have not been thoroughly investigated, and no definitive conclusions can be drawn. More robust, prospective research is needed to better understand dupilumab's role in the unmasking or progression of CTCL.

CONCLUSIONS

Although several studies suggest an association between dupilumab and CTCL, most are anecdotal, retrospective, or limited by confounding variables such as misdiagnosis or history of severe AD. Our review indicates that these associations are more likely due to misdiagnosed AD or the unmasking of preexisting CTCL, as supported by the predominance of literature favoring this explanation over a causal link. Until higher-quality, prospective data emerge, we do not believe dupilumab use should be limited due to concern about CTCL risk, particularly given its efficacy in treating chronic inflammatory diseases.[3] However, CTCL should be carefully ruled out before initiating treatment with dupilumab whenever there is clinical suspicion.

DISCLOSURE

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