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Progression of Cutaneous T-Cell Lymphoma after dupilumab: Case review of 7 patients

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Dupilumab is a fully human monoclonal antibody that binds the interleukin-4 receptor alpha (IL-4R) subunit and inhibits signaling of IL-4 and IL-13. It was approved by the Food and Drug Administration for the treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescents with efficacy in reducing pruritus.[1] The two most common subtypes of cutaneous T-cell lymphoma (CTCL) are mycosis fungoides (MF) and Sézary syndrome (SS). MF/SS and AD are similarly driven by T-helper 2 (TH2) cytokine profiles[2] and may present with similar morphology (i.e. erythema, lichenification, fissuring) with pruritus,[3] disruption of the skin barrier, and impetiginization. Thus, it has been hypothesized that dupilumab may be effective in treating CTCL.[4]

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We performed a chart review of 7 patients (3 female; median age=65.5 years [range 40–77]). Dupilumab was initiated for clinically presumed AD in four patients and used off-label for CTCL (stages IB-IIIB) with severe pruritus in three patients (median duration=4 months [range 3–27]) (Table I). Six of seven experienced initial improvement (median duration=2 months [range 1–8]), followed by worsening body surface area (BSA) (n=7), pruritus (n=5), lymphadenopathy (n=3), and systemic symptoms (n=3). The four patients with clinically presumed AD were eventually diagnosed with CTCL after dupilumab. The three patients with existing CTCL prior to dupilumab developed worsened blood involvement on flow cytometry and were diagnosed with Sézary syndrome while on treatment. Two of the three died of disease progression (Supplement 1).

The initial improvement may be from the transient blockage of Th2 inflammation with shifting to a Th1 tumor-suppressive effect via secretion of interferon-γ, however the nature of subsequent events is unknown.[5] One theory behind the worsening could be from the progression of the malignant T-cell clone being directly linked to the depletion of tumor-suppressive, tumor infiltrating lymphocytes. Alternatively, tumor cells may also escape targeting by dupilumab and lead to emergence of a dupilumab-resistant clone. We postulate that some CTCL cells may be resistant to IL-4 and IL-13 blockade, and it is possible that our cohort happened to be a selective subset of CTCL patients that were largely resistant to the IL-13 and IL-4 blockade. However, we have not seen a single case of lasting improvement with dupilumab use in our CTCL patients, or in the scattered case reports in the literature (Supplemental references).

While dupilumab seems to temporarily relieve pruritus and erythema, our experience suggests that long-term use leads to worsening or progression of CTCL. Our observations highlight the need for caution when using dupilumab in patients with atypical dermatitis presentations without prior exclusion of CTCL via skin biopsy, testing for TCR gene rearrangement, and flow cytometry of the blood. Warning signs suggestive of CTCL for patients with presumed atopic dermatitis while on dupilumab therapy include new eczematous plaques in locations different than original sites, worsening pruritus, lymphadenopathy and new onset moderate-severe “atopic dermatitis” in the elderly. As dupilumab becomes more commonplace in the treatment of AD and atopic disease, we anticipate seeing a greater number of cases of unmasked CTCL in patients initially diagnosed with atypical AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

Patient characteristics and response to dupilumab therapy

Case	Sex/ Age (y)	Diagnosis prior to dupilumab	Total treatment time on dupilumab (months)	Concomitant therapies	Length of time improved on dupilumab (months); description of initial improvement	Worsening on dupilumab	Sezary cell count	Outcome upon discontinuation of dupilumab
1	M/64	Presumed AD (Retrospectively diagnosed as CTCL-NOS Stage IB)	**8**	Azathioprine (PO). Diphenhydramine (PO) Gabapentin (PO), Glucocorticoids (T) Prednisone (PO)	1; Decrease in BSA (40% to 32%$^{+}$) and pruritus	Palmoplantar desquamation, severe skin burning/pruritus, development of erythroderma (BSA 95%), impetiginization with *S. aureus*	N/A	PD (CTCL-NOS Stage IIIA), Improvement with radiation, bexarotene, and interferon-alpha.
2	M/72	Presumed AD	**4**	Methotrexate (PO)	1.5; Decrease in BSA (80% to 60%) and pruritus	Thickening of plaques with superimposed papules	N/A	MF Stage IB, Improvement with NBUVB and topical corticosteroids.
3	F/59	Presumed AD	**27**	Gabapentin (PO), Glucocorticoids (T) Non-medication emollient(T), Tacrolimus(T)	8; Decrease in BSA neck down (40% to 5%), decreased pruritus	Enlargement of facial plaque and onset of fatigue and weight loss	N/A	MF Stage IA, Dupilumab continued at longer intervals (300mg every 3.5 weeks) given patient preference and atopic benefits.
4	F/40	Presumed AD	15	Pantoprazole (PO), Montelukast (PO), Mirabegron (PO)	4; Decrease in BSA (unclear %)	Development of erythroderma, blepharoconjunctivitis, worsening pruritus	N/A	MF Stage IIIA, improvement with prednisone taper, triamcinolone, methotrexate, and NBUVB.
5	M/67	MF Stage IIIB	**3**	Bexarotene (PO), Hydroxyzine(PO), Interferon-γ (IM), Glucocorticoids (T), Prednisone (PO), Pregabalin (PO)	2; Decrease in BSA(80%$^{+}$ to 60%$^{+}$), decreased pruritus	Palmoplantar desquamation, increase in BSA (100%), LAD, worsening pruritus, fatigue, impetiginization with 5. *aureus*	575/uL*, 1022/uL**	PD (MF/SS Stage IVA) and death.
6	M/58	MF Stage IIA	**3**	Bexarotene (PO), Chlormethine(T), Intravenous Immunoglobulin (IV), Glucocorticoids (T), Tacrolimus(T)	1.75; Improved asthma and mild decrease inBSA(15%$^{+}$ to 13%$^{+}$)	Increase in BSA (60%$^{+}$), development of LAD, worsening pruritus, fatigue.	<100/uL*, 6,000/uL**, 9,000/uL***	PD (MF/SS Stage IVA) and death.
7	F/77	MF Stage IB	**3**	Non-medication emollient (T), Glucocorticoids (T)	0;N/A	Development of erythroderma (BSA 80%) and LAD, worsening pruritus	1150/uL**, 1296/uL***	PD (MF/SS Stage IVA), endocarditis, partial response with romidepsin.

BSA, body surface area; IM, intramuscular; IV, intravenous; LAD, lymphadenopathy; MF, mycosis fungoides; NBUVB, narrow-band ultraviolet B phototherapy; PO, Oral; PD, Progressive Disease; SS, Sézary syndrome; T, topical.

*pre-dupilumab treatment,

** during dupilumab treatment,

*** after dupilumab treatment.

+ Estimated body surface area from clinical chart.