

Dupilumab-Associated Mycosis Fungoides; A Cross-Sectional Study

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Abstract

Importance: Treating AD with dupilumab, a monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13), may be associated with progression of MF.

Objective: To examine the associations between length of dupilumab treatment, age and sex, and onset of MF.

Design, Setting, and Participants: An institutional data registry and literature search were used for a retrospective cross-sectional study. Only patients with a diagnosis of MF on dupilumab for the treatment of AD and eczematous dermatitis were included.

Exposure: AD patients treated with dupilumab.

Main Outcomes and Measures: The primary outcome was the length of dupilumab exposure, age and sex, and MF onset. Linear correlations (Pearson) and Cox regression analysis were used to assess the correlation and the risk.

Results: Five eligible patients were identified at our institution. In addition, the PubMed review identified an additional 20 patients. The median age was 58 years, with 42% female. Disease history was significant for adult-onset AD in most patients (n=17, 65.4%) or recent flare of AD previously in remission (n=3, 11.5%). All patients were diagnosed with MF, and one patient progressed to Sézary syndrome while on dupilumab, with an average duration of 13.5 months of therapy prior to diagnosis. Tumor stage was described in 19 of the cases and ranged from an early-stage disease (IA) to advanced disease (IV). Treatment strategies included narrow-band UVB therapy, topical corticosteroids, brentuximab, praladextrate, and acitretin. Male gender, advanced-stage disease, and older age correlated significantly with the hazard of MF onset and a shorter time to onset during dupilumab treatment.

Conclusion and Relevance: Our results suggest a correlation between the duration of dupilumab treatment and the diagnosis of MF, the higher MF stage at diagnosis the shorter the duration of using dupilumab to MF onset. Furthermore, elderly male patients appeared to be more at risk as both male gender and older age correlated with hazard of MF diagnosis. The results raise the question as to whether the patients had MF misdiagnosed as AD that was unmasked by dupilumab or if MF truly is an adverse effect of treatment with dupilumab. Close Monitoring of these patients and further investigation of the relationship between dupilumab and MF can shed more light into this question.

Introduction

Dupilumab is a monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD).¹ Mycosis fungoides (MF) and Sézary syndrome (SS) are the two most common cutaneous T-cell lymphomas (CTCL).² AD, MF, and SS are believed to be driven by T-helper 2 responses.³ Thus, it has been hypothesized that dupilumab may also be efficacious in treating MF and SS.⁴ However, several recent reports have described cases of new-onset MF following treatment with dupilumab with progression to SS in rare cases.³ AD and early stages MF may be similar both clinically and histopathologically. Early-stage MF is likely misdiagnosed as AD with the pivotal possibility of dupilumab promoting the transformation of AD into MF in these patients.^{5,6} Dupilumab may well serve as a catalyst for the progression of MF.⁵ Our aim was to investigate the relationship between dupilumab useage for AD and the development of MF through a retrospective analysis of five patients from our institution and 20 patients were reported in the literature that were diagnosed with MF/SS following dupilumab therapy for AD.

Methods

An institutional data registry was used to conduct a retrospective chart review of patients who develop MF/SS while on treatment with dupilumab for AD between 2015 and 2022. Charts of identified patients were reviewed to extract clinical details, age, sex, past medical history, indication of dupilumab treatment, duration of dupilumab treatment, diagnosis, stage, flow cytometry, TCR gene arrangement, and other treatments. Institutional review board approval was given. A database search of PubMed was performed on June 23rd, 2022 using the search terms "Mycosis fungoides," and "dupilumab". Full article texts were reviewed. Reference lists were screened for additional articles. Patient details were extracted from published articles and entered into a standardized data collection form. We included only cases that report a diagnosis of MF on dupilumab for the treatment of AD and eczematous dermatitis were included. SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) was used to perform linear correlations (Pearson) and Cox regression to assess the correlation and the risk.⁷

Results

Five eligible patients were identified at our institution and additional 20 patients were rendered from PubMed review. Collected patient characteristics are described in **Table 1**. All patients were treated with dupilumab for clinically presumed AD. Disease history was significant for adult-onset AD in most patients (n=17, 70.8%) or recent flare of AD previously in remission (n=3, 12.5%). The median age was 58 years with 42% women (n=10). All patients were diagnosed with MF with one patient progressing to Sézary syndrome while on dupilumab, with an average duration of 13.5 months of therapy prior to diagnosis. Tumor stage was described in 19 patients and ranged from an early-stage disease (IA) to advanced disease (IV).⁸ Treatment strategies included narrow band UVB therapy, topical corticosteroids, brentuximab, praladextrate, and acitretin. Higher stage at the time of diagnosis (**Figure 1**), increased age (**Figure 2**), and male gender (**Figure 3**) correlated with shorter time to MF onset. Patients from our institution demonstrated clinical findings of red erythematous patches and plaques with ichthyosiform scaling, xerosis, and lichenification (**Figure 4**). Compared to pre-dupilumab, post-dupilumab skin biopsies of our five patients revealed an increase in atypical lymphocyte infiltrates tagging the dermoepidermal junction and intraepidermal epidermotropism with dermal fibrosis (**Figure 5**). The atypical lymphocytes were predominantly CD3-positive T-cells with abnormal CD4: CD8 ratios, and rare CD30-positive cells (**Figure 5**).

The results of linear correlations (Pearson) showed an inverse relationship between the stage of MF at diagnosis and the length of dupilumab treatment (i.e. the higher MF stage at diagnosis the shorter the duration of dupilumab to MF onset ($R^2=0.914$, **Figure 1**). Older age patients correlated significantly with decreased time to MF onset ($R^2=0.98$) (**Figure 2**) and Cox regression showed that male gender had a significantly higher risk of MF onset during dupilumab treatment (Log Rank p-value < 0.001) (**Figure 3**).

Discussion

Primary cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas characterized by infiltration of the skin by mature malignant T-cells.⁹ MF and SS are the most common forms of CTCL accounting for around 50% of the primary CTCLs.¹⁰ MF is generally an indolent, progressive monoclonal proliferation of skin-homing memory T-cells with the potential to progress to involve the lymph nodes, blood and viscera.¹¹ MF usually appears in the sixth decade of life with a 1.5-2:1 male/female ratio.¹² There is usually a prolonged clinical course with evolution of skin findings that include scaly erythemic patches or plaques that can progress to tumors and may be localized or disseminated. It often begins as a nonspecific dermatitis or is presumed to be AD, with some postulating dermatitis changing into this T-cell lymphoma by virtue of chronic antigen stimulation.¹³ SS is characterized by the triad of erythroderma, generalized lymphadenopathy and the presence of malignant T-cells with cerebriform nuclei (Sézary cells) in the blood, lymph nodes and skin.^{9,14}

MF and SS show similar features on skin biopsy with epidermotropic lymphoid infiltrates composed of small to medium-sized lymphocytes with cerebriform nuclei.¹⁵ The neoplastic T-cells have a mature T-cell phenotype, CD3+, CD4+, CD45RO+, CD8-. Loss of CD7 or CD5 expression is common.⁸

In 2019 the first reports of Mycosis fungoides following administration of dupilumab for treatment of AD were published.¹⁶ This raised questions and concerns over dupilumab's safety. The Food and Drug Administration approved dupilumab in 2017 for the treatment of moderate to severe AD in adults, which has been shown to have a strong efficacy in improving cutaneous disease and reducing pruritus.¹⁷ Atopic dermatitis (AD) affects approximately 15-20% of children and 1-3% of adults worldwide and is commonly treated with emollients and topical corticosteroids (TCS).^{18,19} However, new therapies such as dupilumab have arisen in recent years. Dupilumab is a monoclonal antibody directed against the IL-4-receptor-alpha subunit, inhibiting the IL-4 and IL-13 pathways. These pathways play prominent roles in inflammation, epidermal barrier dysfunction, and itch in AD.¹

Primary cutaneous T-cell lymphomas (CTCL) lesions have demonstrated a high expression of IL-13 receptors, which lead to hypothesize that dupilumab may also be an effective treatment for mycosis fungoides and Sézary syndrome.^{20,4} However, with the more widespread use of dupilumab therapy in patients with presumed AD, increased cases of MF and SS have been reported. This raises questions of whether there is a role of IL13 in the pathophysiology of dupilumab/MF coincidence. In addition, whether dupilumab is safe in AD patients as well as the many others who use dupilumab off label in various other dermatologic conditions²¹

Multiple theories have been postulated to explain this phenomenon, recognizing dupilumab as a catalyst for the progression of MF. The prevailing theory is that these patients had early-stage MF that was misdiagnosed as AD and that dupilumab exacerbated the MF.⁵ This theory is plausible due to the difficulty of distinguishing AD from early-stage MF both clinically and histologically. MF patients often present with complaints of pruritic scaly patches or generalized erythema similarly to AD. Additionally, patch stage early MF mimics AD with higher proportions of reactive lymphocytes and a smaller proportion of neoplastic T-lymphocytes. Thus, without a high degree of clinical suspicion or classic signs weight loss and lack of atopy, MF may be misdiagnosed as AD. However, the role that dupilumab plays in the evolution of AD into MF remains unknown. One theory behind this worsening is that this specific cohort of patients who later developed MF while on dupilumab had a CTCL resistant to the IL-4 and IL-13 blockade.⁵ Another theory suggests that dupilumab hastens the progression of MF by altering the Th1/Th2 cytokine balance towards a primarily Th1-driven response which is characteristic of early-stage MF.²¹ Others have suggested that dupilumab promotes the malignant transformation of benign lymphoid infiltrates found in AD, leading to MF. This has been supported by the findings of MF evolving from chronic inflammatory states, such as AD.²² Given the many theories, it is apparent that additional studies are warranted to further elucidate the causes and mechanisms behind the phenomenon, which may include additional malignancies including Hodgkin lymphoma and nodal anaplastic large cell lymphoma.^{23,24}

Our results showed an inverse relationship between the stage of MF at diagnosis and the length of dupilumab treatment (i.e. the higher MF stage at diagnosis the shorter the duration of dupilumab to MF onset. Older age patients correlated significantly with decreased time to MF onset and male gender had a significantly higher risk of MF onset during dupilumab treatment. This suggests that specific populations may be more at risk for quicker disease progression and aggressive forms of MF. Thus, close monitoring both clinically and histologically may be warranted in elderly male patients.

Limitation:

Our study reviewed all published MF cases on dupilumab to our knowledge and provided an exploratory correlation analysis. This analysis was based on limited available observational data. Further studies are necessary to fully understand the relationship between age, gender, and duration of dupilumab treatment in patients who develop MF.

Conclusion

Our analysis showed a correlation between the duration of dupilumab treatment, and the diagnosis of MF. In those diagnosed with MF while being on dupilumab, the more advanced the MF stage, the shorter the treatment duration to MF onset. Additionally, older age and male gender appear to have a higher risk of advanced MF stage. This raises the question as to whether these patients had MF underdiagnosed as AD exacerbated by dupilumab or if MF is induced

by dupilumab. Despite dupilumab remaining an effective therapy for MF, close monitoring of elderly men with serial biopsies and close observation of clinical changes may be warranted.

Declarations

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Conflicts of Interest: None declared.

IRB approval status: Approved

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Tables

Table 1: Characteristics of patients diagnosed with Mycosis fungoides or Sezary syndrome following treatment with dupilumab for atopic dermatitis. (PMH: Past medical history, AD: Atopic dermatitis, MF: Mycosis fungoides, Sezary syndrome, TAC: Triamcinolone, nbUVB: narrow-band type-B ultraviolet light: MTX: Methotrexate, RT: Radiation therapy, ECP: Extracorporeal photopheresis). a. Tumor as defined by the 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas.⁸ b.The ISCL/EORTC has suggested a threshold of 30% CD4+/CD26– T cells for staging purposes in MF/SS, but currently no consensus.²⁵ c. Clonal T-cell receptor gene rearrangements are frequently identified in MF skin lesions and may help to differentiate between early MF patches and benign mimics.²⁶ d.Diagnosis as recommended by ISCL classification for primary cutaneous lymphomas.⁸ Diagnosis as recommended by ISCL-EORTC and countersigned in the WHO Classification of Tumors.⁸

Reference	Age	Sex (M/F)	PMH	Indication for dupiluma, duration of symptoms	Duration of dupilumab treatment (months)	Diagnosis	Stage ^a	Flow cytometry blood ^b	TCR gene rearrangements ^c	Treatment
Our case-1	76	M	Unremarkable	AD	12	MF ^d	IIB	CD4+/CD7-population 7%, CD4+/CD26-population 25%	Not reported	TAC, MT, sho, noc
Our case-2	36	M	Unremarkable	AD	2	MF	IB	No concerning cytology	Unable to evaluate because too little DNA	TAC
Our case-3	68	F	Unremarkable	AD	11	MF	IB	No concerning cytology	T-cells + for delta chain	TAC
Our case-4	59	M	Unremarkable	AD	Not reported	SS ^e	IV	Not reported	Aberrant CD4+ T Cell	Not
Our case-5	77	M	Unremarkable	AD	Not reported	SS	IV	Not reported	Not reported	Not
(Ayasse et al. 2020)	64	M	Refractory AD	Adult onset AD, 5 years	2.5	SS		>7,000 CD4+CD26-Sezary cells/mm3	Monoclonal gamma, polyclonal beta	Bex, ECF
(Ayasse et al. 2020)	40	F	Eosinophilic asthma, chronic eosinophilia	AD, flare for 4 years, onset as a child	13	MF	IIB	Not reported	Could not be obtained	Not
(Chiba et al. 2019)	58	M	Carcinoma of maxillary sinus	AD, flare for 9 years, onset as a child	1	MF	N/A	Not reported	Clonal rearrangement	Top, cor, + nl
(Newsom et al. 2021)	48	F	Not reported	AD, 6 years	5	MF	1B	Not reported	Not reported	Not
(Newsom et al. 2021)	55	M	Oropharyngeal cancer	AD, 5 years	6	MF	1B	Not reported	Not reported	Not
(Russomanno and Carver DeKlotz 2021)	43	M	Not reported	AD, flare for 12 months, onset as a child	2	MF	IVA2	Yes, 40% expression of CD30	Not reported	Bre, pra
(Miyashiro et al. 2020)	51	F	Not reported	AD, 1 year	2	MF	Tumoral	No concerning cytology	Not reported	Act, PU
(Hollins et al. 2020)	61	M	Restrictive lung disease, idiopathic CD4 lymphopenia	Eczematous dermatitis, 10 years	Not reported	MF	Not reported	Not reported	Not reported	Not
(Hollins et al. 2020)	52	M	Not reported	Eczematous dermatitis	1.5	MF	Not reported	Not reported	Not reported	Not
(Hollins et al. 2020)	60	F	Not reported	Eczematous dermatitis, 3 years	0.75	MF		Not reported	Not reported	Not
(Sokumbi et al. 2021)	66	F	Not reported	Chronic dermatitis, 6 years	1.2	MF	IIA	Not reported	Negative	Not
(Sokumbi et al. 2021)	65	F	Not reported	Chronic AD, 4 years	2.5	MF	IB	Not reported	Negative	Not
(Sokumbi et al. 2021)	74	M	Not reported	AD, 6 years	24	MF	III	Not reported	Negative	Not
(Sokumbi et al. 2021)	73	M	Not reported	Chronic dermatitis, 5 years	14	MF	III	Not reported	Negative	Not
(Sokumbi et al. 2021)	74	M	Not reported	Chronic dermatitis, 4 years	1	MF	IA	Not reported	Positive	Not
(Sokumbi et al. 2021)	44	F	Not reported	AD, 9 years	12	MF	IV	Not reported	Negative	Not
(Sokumbi et al. 2021)	27	M	Allergic	AD, 7 years	14	MF	IB	Not reported	Insufficient DNA	Not

al. 2021)			contact dermatitis							
(Espinosa et al 2020)	72	M	Rheumatoid arthritis	AD, Over 20 years	4	MF	IB	Small T-cell clone, did not meet criteria for clinically significant blood involvement.	Showed monoclonality in both tissue and blood.	nbl
(Espinosa et al 2020)	59	F	Asthma	AD, since childhood	27	MF	IA	Unremarkable	Negative	Cor dup ag me adv
(Espinosa et al 2020)	40	F	Blood eosinophilia and eosinophilic asthma	AD, 7 years	15	MF	IIIA	Unremarkable	Negative	5-w pre tap tria oini nbl mei

*Patient also received guselkumab for 1 month and cyclosporine for 2 months during treatment timeline for suspected psoriasis on repeat biopsy

Figures

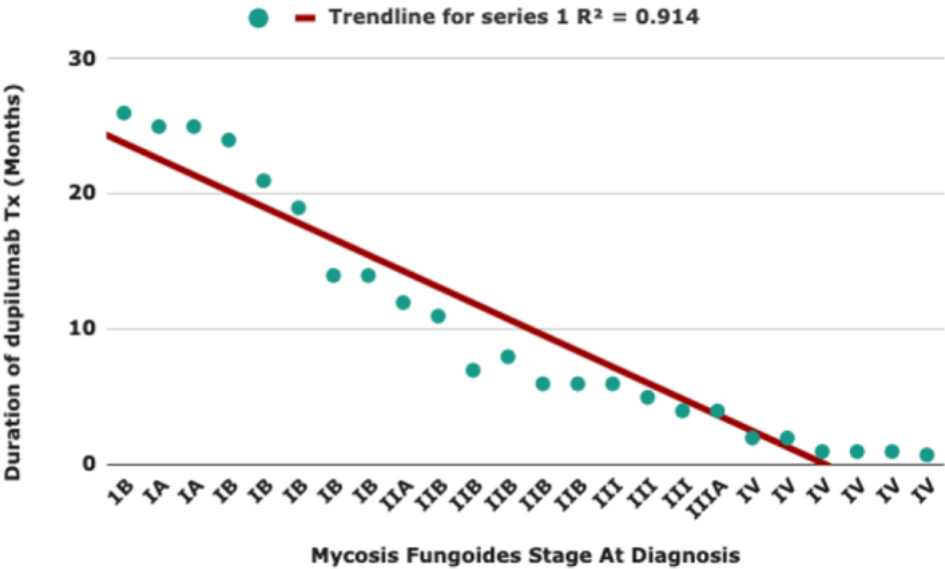


Figure 1

Diagram showing the correlation between increased stage and decrease time to MF onset in Dupilumab patients.

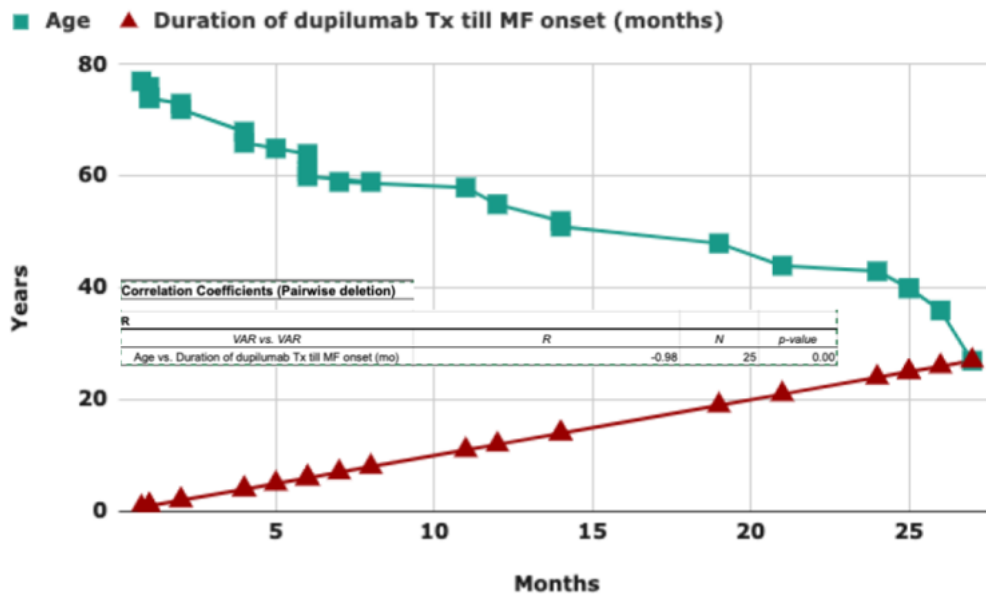


Figure 2

Diagram showing the correlation between increased age and decrease time to MF onset in Dupilumab patients

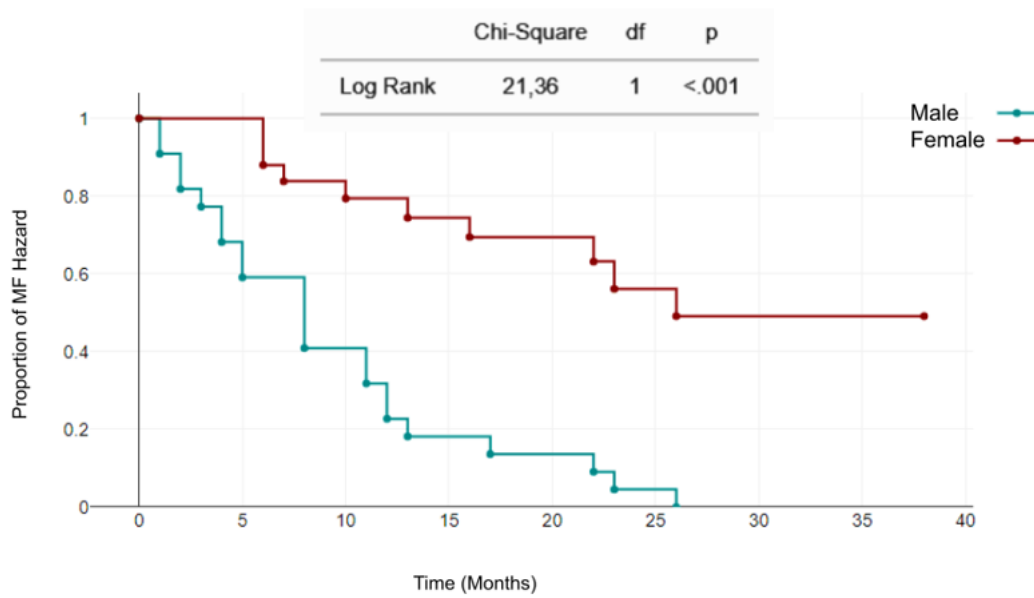


Figure 3

Diagram showing the correlation between male gender and increased MF onset compared to female gender in Dupilumab patients.



Figure 4

Clinical images from our patients showing MF onset in Dupilumab patients. (Image 4A and 4E corresponds to case-2 in Table 1, Image 4B corresponds to case-4 in Table 1, Image 4C and 4F corresponds to case-1 in Table 1, image 4D and 4G corresponds to case-5 in tabel 1)



Figure 5

Examples of skin biopsies from our Dupilumab patients showing MF histology and immunoprofile.