



2020 Research Report

Cutaneous Lymphoma Foundation: Fostering Research Now and Into the Future

In 2019-2020, we proudly awarded four \$1,500 Young Investigator Travel Awards, four \$50,000 Cutaneous Lymphoma Catalyst Research Grants, and continued work on our 2022 and beyond long-term research roadmap. Together, with you, we are making an impact in cutaneous lymphoma research with over \$200,000 in funding awarded in 2019-2020!

Since 2003, the Cutaneous Lymphoma Foundation has been providing young investigator travel awards to help researchers early in their career attend and present their work at medical meetings around the world. This year, we were proud to offer four of these travel awards:

- Two for the Society for Investigative Dermatology (SID)
- One for the American Society of Hematology (ASH)
- One for the European Organisation for Research and Treatment of Cancer - Cutaneous T-Cell Lymphoma Task Force (EORTC-CLTF)

In this publication, you'll have an opportunity to review their award winning abstracts.

Last year we announced the launch of our new Cutaneous Lymphoma Catalyst Research Grant as part of our overall Research Awards Program. This grant was crafted to offer two grants each year with the purpose of advancing or bridging an existing cutaneous lymphoma research project. We are thrilled that the Leukemia & Lymphoma Society has partnered with us to double the impact, allowing four \$50,000 grants to be awarded this year!

In the inaugural year of the Cutaneous Lymphoma Catalyst Research Grant, we received many highly qualified applications from around the world. Summaries of the work being completed by the awardees of the 2020 Cutaneous Lymphoma Catalyst Research Grant can be found in the following pages.

Finally, the Cutaneous Lymphoma Foundation Board of Directors, along with our Research Advisory Council, have been hard at work developing a plan to ensure the biggest impact is made to help achieve the vision of **a life free of cutaneous lymphoma!** Stay tuned, and be on the lookout for the research roadmap announcement coming soon – the long-term plan for how together we will support research and researchers in cutaneous lymphoma.



Research Advisory Council pictured from left to right: (Front Row) Stuart Lessin, MD; Susan Thornton, CEO; Pierluigi Porcu, MD (Co Chair). (Back Row) Jaehyuk Choi, MD, PhD; Bradley Haverkos, MD, MPH; Michael Yaffe, PhD (LLS); Christine Eischen, PhD (Co Chair); Rick Winneker, PhD (Consultant) and Anjali Mishra, PhD. (Not pictured: Laura McGirt, MD; Christopher Shipp, Patient; Alison Moskowitz, MD; Alejandro Gru, MD; Steven Jones, MD, Patient; and Michael Khodadoust, MD, PhD.)

Award Recipient - Funding Year 2020

Single-Cell Transcriptome Analysis of IL-4R α -Positive Cells in Mycosis Fungoides Skin Tumors

Mycosis Fungoides (MF) is the most common form of cutaneous T-cell lymphoma, a cancer that mainly affects skin but which can also affect blood and internal organs as the disease advances. In the early stages, the skin of MF patients can look like common and benign conditions such as eczema or psoriasis, making diagnosis uncertain and leading to delays in treatment and reduced life expectancy. This project aims to discover markers of MF that can be used for reliable diagnosis and consequently rapid treatment, as well as other markers useful in designing and monitoring treatment. Focusing on interleukin-13 (IL-13), a protein produced by tumor cells to help them grow, we will employ innovative technologies to find other tumor-specific proteins that interact with IL-13. We expect that each patient may have a unique set of IL-13-associated proteins, which means that the most effective therapy must be designed specifically for each patient. Such personalized therapy should increase the likelihood of patients responding with increased survival rates.

Project objectives/goals. The pattern of cytokine production in the skin tumor microenvironment (TME) is considered to be of major importance for the pathogenesis of MF, enhancing proliferation of the malignant cells and/or depression of the anti-tumor immune response. We have recently shown that IL-13 and its receptors are highly expressed by tumor cells in the skin lesions of MF patients and that IL-13 synergizes with IL-4 in inducing tumor cell growth. Cytokines IL-4 and IL-13 share a common signaling receptor subunit, IL-4R α . Thus, IL-4R α expression by malignant lymphocytes and by immune and stromal cell in the TME plays a crucial role in MF pathogenesis. The aims of this proposal take advantage of recent advances in single-cell RNA-sequencing to study the role of IL-4R α in the pathogenesis of MF. The outcome of this study will have a **significant impact** on improving diagnosis and personalized disease management by understanding tumor heterogeneity at the single-cell level and will open avenues for tailoring therapy to specific patients. The molecular understanding

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of MF pathogenesis will be advanced by identifying critical pathways that are activated in IL-4R α + malignant cells and by characterizing the distinct TMEs around IL-4R α + non-malignant cells that foster cancer development and progression. Further, the high-resolution profiling of tumor cells is expected to reveal new targets for highly specific therapeutic intervention that may be tailored to subsets of patients such as those responsive to anti-IL-4R α therapy.

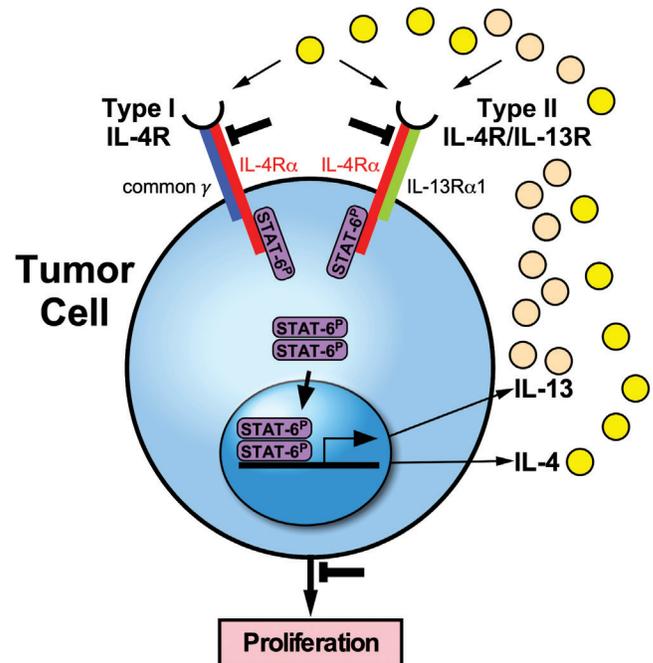


Figure legend. Tumor lymphocytes produce IL-4 and IL-13 and express their signaling receptors. IL-4 binds to both type I IL-4R and type II IL-4R/IL-13R, while IL-13 binds only to type II IL-4R/IL-13R. The IL-4R α subunit is common to both type I and type II receptors. Engagement of the receptors activates STAT-6 (pSTAT-6) and induces proliferation of tumor cells. Pharmacological inhibition of IL-4R α inhibits tumor cell proliferation.

Award Recipient - Funding Year 2020

Synergistic Therapy with JAK Inhibition for the Treatment of Advanced CTCL

Advanced cutaneous T cell lymphoma (CTCL) with blood involvement, including the mycosis fungoides and Sézary syndrome subtypes, is associated with a worse prognosis, and responses to currently available treatments are limited. There clearly remains an unmet need for more effective and novel approaches to therapy in this cancer. Through comparative hybridization genomic and exome sequencing analyses, we and others have elucidated the numerous and varied genetic alterations across CTCL patient cells, helping in part to explain why single drug targeting strategies are not universally effective for all patients.

Despite the wide genetic variation in CTCL cells, specific common pathways nonetheless appear to drive the behavior of the CTCL cells across different patients: (1) prolonged T cell activation, (2) resistance to cell death, and (3) uncontrolled gene expression. More specifically, these alterations suggest T cell signaling pathways through Janus kinase proteins (JAK), antiapoptotic protein B-cell lymphoma 2 (BCL2), and transcriptional regulators bromodomain and extra-terminal (BET) as targetable proteins in CTCL. For select genes of interest, we sorted patient CTCL cells and compared them to CD4+ T cells isolated from healthy people to reveal marked differences in the levels of several such targets (Figure. 1).

We believe that more effective treatment strategies can be constructed by empowering novel combination therapies to simultaneously uncouple these pathways, possibly also using lower doses of individual agents that act synergistically against the malignant cells and decreasing the risk of drug resistance. Which combinations would be most, and more generally, effective against CTCL cells remains a critical question. To address this, we are leveraging an automated robotic, micro-fluidic, acoustic non-touch drug-screen platform at the Yale Center for Molecular Discovery, substantially improving the efficiency of live patient sample testing for sensitivity to current and cutting-edge anti-CTCL agents, alone and in combination. Under this

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effort, we have already elucidated the potential of targeting of BCL2 (*Blood*, 2017; recently initiated clinical trial at Yale) and BET (*Oncotarget*, 2018) in the treatment of CTCL. Furthermore, combining JAK-inhibition with BET-inhibition or BCL2-inhibition appears to provide a marked synergistic effect against the CTCL cells. We will further study this therapeutic strategy using robotic drug screening and complimentary molecular analyses to elucidate the relevant pathways underlying CTCL, with the ultimate goal of developing novel synergistic treatments for CTCL patients with advanced disease.

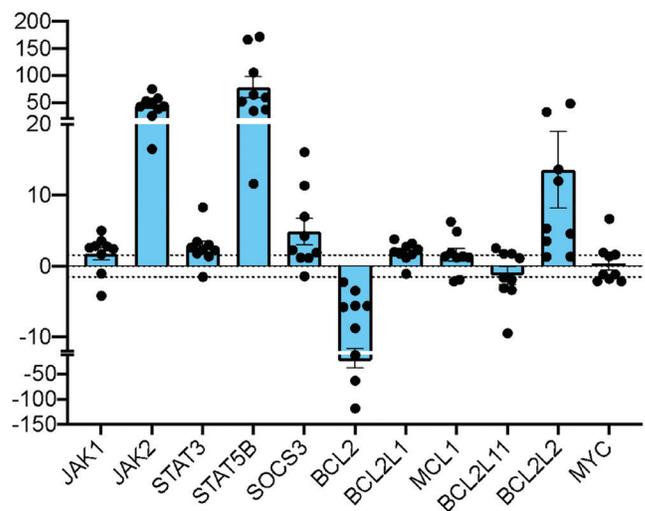


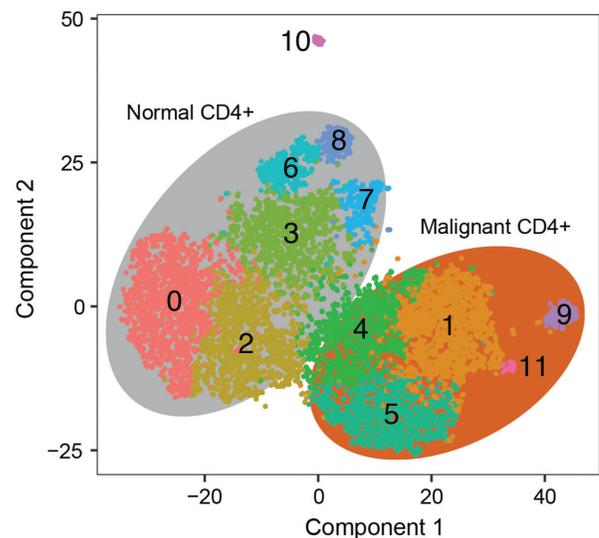
Figure 1. RT-PCR expression levels of isolated patient CTCL cells relative to healthy control CD4+ cells. For select genes of interest, we sorted patient CTCL cells and compared them to CD4+ T cells isolated from healthy controls to reveal marked differential expression by qRT-PCR of several targetable genes/ products, including JAK2 (>50x), STAT3 (>2x), STAT5B (>50x), and BCL2 (>20x) – unpublished data.

Award Recipient - Funding Year 2020

Extension of Single Cell RNA-Sequencing-Based Analysis of Cutaneous T Cell Lymphomas to Skin-Infiltrating Cells

The most common form of cutaneous T-cell lymphoma (CTCL) is called mycosis fungoides (MF), and MF patients usually present with small red patches of skin due to the lymphoma. While most cases of MF stay in the skin, some patients will go on to develop more severe disease as the lymphoma spreads to the blood, lymph nodes, and internal organs. Sézary syndrome (SS) is another form of CTCL in which the lymphoma has spread to all, or nearly all, of the skin and can already be found in the blood. Treatments for SS and advanced MF may initially decrease the amount of lymphoma in the body, but most often the given treatment stops working. We hypothesized that the population of lymphoma cells in a patient consists of smaller subpopulations, one or several of which may be resistant to a given treatment and will outgrow the other subpopulations. Using a technique called single cell RNA-sequencing, we have been able to show that the lymphoma population found in the blood is made up of several closely related but distinct subpopulations that express different patterns of genes. Facilitated through funding from the Cutaneous Lymphoma Foundation and through a collaboration between CTCL experts at the University of Iowa and Mayo Scottsdale, we plan on extending our initial analysis to a larger number of SS blood samples, as well as to address CTCL populations in the skin, with

the goal of identifying relationships between the lymphoma cells in the circulation and those in the skin. In addition, we propose to look at differences in the lymphoma cells in the skin of patients with early and advanced stage MF using the same techniques. We submit that these studies will increase our understanding of CTCLs and may help determine the best treatment strategies for MF and SS.



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Award Recipient - Funding Year 2020

Characterization of the skin microbiome in cutaneous T cell lymphoma

Cutaneous T-cell lymphoma (CTCL) is the most common type of skin lymphoma. Patients with advanced disease often suffer from, and die of, infections. Certain bacteria can drive CTCL progression. This study will characterize the bacterial composition in the affected skin of different CTCL disease stages and also determine if decreased bacterial diversity is associated with more advanced and refractory disease.



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2019 American Society of Hematology (ASH) Award Recipient

Diagnostic 2-Gene Classifier in Early-Stage Mycosis Fungoides: A Retrospective Multicenter Study

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Introduction: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma and represents more than 50% of all primary cutaneous lymphomas. It is typically an indolent disorder with limited patches and plaques. One third, however, experience progression with ulcerating tumors and possible further systemic dissemination. Currently, the diagnosis of MF is based on clinical and histological examinations, but this has proven, especially in early-stage disease, to be challenging due to similarities with several benign skin conditions such as psoriasis, pityriasis lichenoides chronica, and dermatitis. Despite intensive research, reliable diagnostic biomarkers for early-stage MF are still needed. This study aims to identify a diagnostic classifier that could support the diagnostic workup leading to an exact diagnosis in the early-stage of this complex and potentially lethal disease.

Methods: We analyzed 43 formalin-fixed and paraffin-embedded (FFPE) skin biopsies from 36 patients with early-stage MF. Seven patients had 2 longitudinal biopsies available for analysis. These were compared with FFPE skin biopsies from patients with unspecified dermatitis (n=29) and healthy skin (n=12). All samples were collected from the archives of the Department of Pathology, Region Zealand, Denmark in the period 1990-2016. The histological

samples were revised and clinical records were reviewed to establish the diagnosis and stage for each patient. Total RNA was extracted from ten 10- μ m sections of FFPE tissue, and 50-100 ng of RNA was analyzed on the NanoString nCounter platform by applying the Myeloid Innate Immunity Panel, which quantifies the expression of 800 immune related genes. Differentially expressed genes (DEG, 2-fold change, $p < 0.05$), were assessed by ANOVA, and a Support Vector Machine (SVM) diagnostic classifier was built based on 2-10 DEG and evaluated by 10-fold cross-validation. The classifier was tested on an independent, early-stage MF patient cohort (n=27). Protein expression was validated with immunohistochemistry and digitally analyzed by applying a specifically designed algorithm with the Leica Tissue IA 2.0 software. Double immunofluorescence staining protocols were developed to identify subtypes of TRAF1 positive cells in combination with various macrophage/dendritic cell markers (CD168, CD63, CD11c, CD1a, CD14, and S100) as well as T-cell (CD3) and B-cell (CD20) markers.

Results: A diagnostic classifier consisting of TOX and TRAF1 was able to distinguish early-stage MF from dermatitis with an overall accuracy of 85% in the discovery cohort and 80% in an independent validation cohort. *continued on page 6*

Thank you to all of our generous donors, sponsors and partners for your support in making an impact in cutaneous lymphoma research.



LEUKEMIA & LYMPHOMA SOCIETY®

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Thank you to the physicians who served on this year's Scientific Review Councils:

Jaehyuk Choi, MD, PhD (Chair)
Northwestern University

Michael Khodadoust, MD, PhD
Stanford University School of Medicine

Pierluigi Porcu, MD
Thomas Jefferson University

Stuart Lessin, MD, Committee Chair (Co-Chair)
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Steven Horwitz, MD
Memorial Sloan Kettering Cancer Center

Thomas Kupper, MD
Brigham and Women's Hospital

Anjali Mishra, PhD
Thomas Jefferson University

Youn Kim, MD
Stanford Cancer Institute

Diagnostic 2-Gene Classifier...continued

TOX and TRAF1 protein levels were significantly elevated in early-stage MF compared to the dermatitis group ($p < 0.0001$). TOX and TRAF1 were also significantly increased in the progression from early-stage MF to tumor stage MF ($p=0.003$ and $p=0.004$, respectively). Subtypes of TRAF1-positive dendritic cells in early-stage MF consisted primarily of S100+ cells in both the epidermal and dermal compartment. A few TRAF1+ cells in the Pautrier microabscesses stained double positive with CD11c. In tumor stage MF the majority of TRAF1+ dendritic cells counterstained with CD1a and CD11c. Both neoplastic and reactive T-lymphocytes (CD3+) expressed TRAF1 in a minor degree in early-stage MF, whereas T-cells in tumor stage MF expressed TRAF1 in much higher degree and the majority of the neoplastic T-cells were TRAF1 positive. No macrophages (CD68+ or CD163+) or B-cells double stained with TRAF1.

Conclusion: In the present study, we developed a two gene

mRNA diagnostic classifier discriminating early-stage MF from dermatitis. The protein expression level of TOX and TRAF1 confirmed our gene expression levels and identified a highly significant difference between early-stage MF and dermatitis, which can prove useful in diagnostics of early-stage MF.

Additional Credits: Nielsen PR.^{1,4}, Eriksen JO.¹, Lindahl LM.², Wehkamp U.³, Andersen G.¹, Bzorek M.¹, Grønbaek K.⁴, Ødum N.⁵, Litman T.⁵, Gjerdrum LMR.¹

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2019 Society for Investigative Dermatology (SID) Award Recipient

CCR4 expression in CD8+ cutaneous T-cell lymphomas and lymphoproliferative disorders and its implications for diagnosis and treatment

CD8+ cutaneous lymphomas include a variety of rare cutaneous T-cell lymphomas (CTCL) and lymphoproliferative disorders (LPD) with distinctly different prognoses, clinicopathological overlap, and resistance to current therapeutic strategies. Improved diagnostic tools and therapeutic options are needed. To evaluate C-C chemokine receptor 4 (CCR4) expression in CD8+ CTCL/LPDs as a diagnostic and potential therapeutic biomarker we performed CCR4 immunohistochemistry (IHC) on formalin-fixed paraffin-embedded skin sections from 41 patients with various CD8+ CTCL/LPDs ($n=49$ biopsies). The percent of CCR4+ cells within the atypical lymphoid infiltrate, the staining intensity and pattern were evaluated. We correlated IHC results with clinicopathologic diagnoses: CD8+ mycosis fungoides (MF, $n=14$), aggressive epidermotropic CD8+ T-cell lymphoma (AETCL, $n=8$), subcutaneous panniculitis-like T-cell lymphoma (SPTCL, $n=7$), CD30+ LPD ($n=6$), primary cutaneous $\gamma\delta$ T-cell lymphoma (GDTCL, $n=6$) and other CD8+ CTCL/LPD subtypes ($n=8$). We found that 34/49 (69%) of cases and 30/41 (73%) of patients showed any CCR4 expression. CCR4 was expressed differentially between variants of CD8+ CTCL/

LPD: CCR4+ cells were seen in all MF cases, with 79% showing high expression level ($>25\%$ of the infiltrate). MF patients with more advanced disease had higher CCR4 expression. Any CCR4 positivity was also noted in 83% of CD30+ LPD, 75% of AETCL, 33% of GDTCL and none of SPTCL cases. However, high CCR4 expression was demonstrated in only 33%, 17%, 12.5%, and 0% of CD30+ LPD, GDTCL, AETCL and SPTCL, respectively. In conclusion, CCR4 IHC may be diagnostically helpful in the evaluation of CD8+ CTCL/LPDs, particularly in distinguishing advanced CD8+ MF from aggressive CD8+ CTCL. The consideration of recently FDA-approved anti-CCR4 treatment (i.e. mogamulizumab) for MF and Sezary syndrome in CD8+ MF is supported by our results. The role of these therapies in other CD8+ CTCL/LPDs is not yet clear.

Additional Credits: AUTHORS (FIRST NAME, LAST NAME): Shamir Geller^{1,2}, Travis J. Hollmann¹, Steven M. Horwitz¹, Patricia L. Myskowski¹, Melissa Pulitzer¹

INSTITUTIONS (ALL): 1. Memorial Sloan Kettering Cancer Center, New York, NY, United States. 2. Tel Aviv Medical Center, Tel Aviv, Israel.



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2019 Society for Investigative Dermatology (SID) Award Recipient

Epidemiology of primary cutaneous gamma/delta T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma in the United States from 2006-2015: A Surveillance, Epidemiology, and End Results-18 analysis

Primary cutaneous gamma-delta T-cell lymphoma (pcGDTCL) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL) are two very rare primary cutaneous lymphomas that present with multifocal subcutaneous nodules. Until 2005, these were grouped together as SPTCL, complicating our understanding of epidemiologic and survival data for these two malignancies. We use Surveillance, Epidemiology, and End Results 18 (SEER-18) data to compare the incidence, demographics, and survival of these two lymphomas in patients diagnosed from 2006-2015 across the United States, in an attempt to deconvolute this data. We identified 37 cases of pcGDTCL and 132 of SPTCL diagnosed between 2006-2015. The cumulative incidence of pcGDTCL, 0.40 per 10 million (95% CI 0.28-0.56 per 10 million), was significantly lower than that of SPTCL at 1.51 per 10 million (95% CI 1.26-1.80 per 10 million; $p < 0.05$). Patients with pcGDTCL were significantly older than those with SPTCL (median 63 years vs. 45 years;

$p < 0.001$) and more likely to be male ($p < 0.013$). Cox proportional hazards modeling revealed that patients with pcGDTCL were at significantly higher risk of death than patients with SPTCL (HR 5.00, 95% confidence interval [CI] 1.8-14.3, $p = 0.005$). Increasing age (HR 1.31 per 10 years, 95% CI 1.0-1.7, $p = 0.04$) and stage (HR 1.52, 95% CI 1.05-2.1, $p = 0.023$) were also significant factors. Limitations of sample size and diagnostic accuracy may underestimate the aggressive nature of pcGDTCL in this report. In conclusion, pcGDTCL has a markedly worse prognosis than SPTCL. Patients with pcGDTCL are more likely to be male and older in age than those with SPTCL. This should allow clinicians to build a more accurate differential diagnosis for patients with lymphocytic panniculitis, and more accurately prognosticate clinical outcomes.

Additional Credits: Kavita Goyal MD, Kimberly Bohjanen MD, and David Pearson MD



Amrita Goyal, MD

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2019 European Organisation for Research and Treatment of Cancer - Cutaneous T-Cell Lymphoma Task Force (EORTC-CLTF) Award Recipient

Response to topical corticosteroid monotherapy in mycosis fungoides

Although topical corticosteroids are widely used to treat mycosis fungoides (MF), data on response rates to their use as monotherapy in MF are limited. We tested the efficacy of topical corticosteroid monotherapy for MF, comparing gender, age and stage distributions between patients who did or did not improve. An institutional review board approved retrospective review was conducted using our MF patient database. Patients with biopsy proven MF, ranging from stage IA to IVA, who received topical corticosteroid monotherapy were included in the study. Response rates were determined by percent change in body surface area (BSA) involvement from the first visit over time.

Of the MF patients in our database, 24% (39/163) initially received topical steroid monotherapy. 29 patients (74%) had an

improvement in BSA, with an average decrease of 64% between the first and second visits. 10 patients (26%) did not improve or progressed with an average increase of 51.6% in BSA over 21.8 weeks. 12 patients (31%) had a complete response (BSA involvement 0%) with prolonged topical steroid use. Female gender and early stage MF were more represented in patients who did respond to topical steroids. Our data demonstrate the efficacy of topical steroids in early stage MF patients with a measurable difference in BSA involvement. Topical steroids alone can achieve complete remission in a limited subset of patients with early stage MF.

Additional Credits: Doaa Shalabi, Megan O'Donnell, Pierluigi Porcu, Neda Nikbakht



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