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Low-dose Psoralen–UV-A maintenance therapy prolongs disease-free remission rates in mycosis fungoides patients

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ABSTRACT A clinical decision report using Vieyra-Garcia P, Fink-Puches R, Porkert S, et al. Evaluation of Low-Dose, Low-Frequency Oral Psoralen–UV-A Treatment With or Without Maintenance on Early-Stage Mycosis Fungoides. *JAMA Dermatology*. 2019;155(5):538. https://doi.org/10.1001/jamadermatol.2018.5905 for a patient weighing whether to continue treatment in light of socioeconomic circumstances.

Keywords: *mycosis fungoides, PUVA, maintenance*

Clinical Context

Maria Johnson (pseudonym) is a 47-year-old African American female, with no significant past medical history, presented to the dermatology clinic with complaints of pruritic hypopigmented patches on her back, abdomen, and arms for the past year. Ms. Johnson expressed dissatisfaction with the appearance of her skin, and stated that it is affecting her personal life, and finds herself frequently trying to cover up her skin. She is also having more trouble sleeping as of late due to the constant pruritic nature of her lesions.

Two biopsies were taken from the patient and histology results revealed a diagnosis of stage IA mycosis fungoides. Ms. Johnson wanted to have discussions about the best treatment options, however, was worried due to her financials constraints. She had recently lost her job and was trying her best to support her children even before considering additional health care costs. The doctors were able to work with insurance and advocate for the patient to effectively get her a treatment plan that would best suit the severity of her condition. Ms. Johnson was started on a treatment of Psoralen–UV-A (PUVA) photochemotherapy twice weekly for 10 weeks, and she began to see a very promising positive response. This prompted a discussion between Ms. Johnson and her physician about the length of treatment for her condition. She had expressed some concerns about continuing treatment any longer, because she was worried about the dangers of exposing her skin to additional UV light given her family history of skin cancer. She also was having trouble commuting to the office to get the physical treatment several times a week due to her socioeconomic situation; she was without a vehicle and was traveling to her appointments via friends or public transportation. Although her physician recommended maintenance therapy due to risks of recurrence, Ms. Johnson wanted to take some time to weigh her options moving forward. The physician made sure to reassure the patient that her concerns had been heard and that he would try his best to help alleviate these worries and try to connect Maria to the proper resources to help her get the best care. She needed to weigh the benefits of treatment with the risks of harm and her struggles with access to care. Maria did not want to compromise her health because of the unfortunate social situation she was in, and she wanted to be around for her family for a long time, therefore her primary concern was minimizing risk of reoccurrence. Given her clinical

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context, maintenance light therapy was still the recommendation, though there remains some disagreement about the benefits and its use varies from institution to institution.

Clinical Question

In patients with early-stage Mycosis Fungoides, is the addition of low-dose, low-frequency oral PUVA maintenance therapy superior to induction therapy alone?

Research Article

Vieyra-Garcia P, Fink-Puches R, Porkert S, et al. Evaluation of Low-Dose, Low-Frequency Oral Psoralen–UV-A Treatment With or Without Maintenance on Early-Stage Mycosis Fungoides. *JAMA Dermatology*. 2019;155(5):538.
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Related Literature

In order to gain a baseline understanding of current management strategies of patients diagnosed with mycosis fungoides (MF), a search on UpToDate for "mycosis fungoides treatment" was conducted. MF is relatively rare, with an incidence rate of 0.36 per 100,000 person years and often presents in people aged 45 to 60 years.[1] For patients with early stages of the disease, it is recommended to use skin directed therapies. It has become standard practice to use psoralen plus UVA phototherapy as a first line treatment modality in early-stage cases of MF. Psoralen is taken up by epidermal cells and creates toxic DNA adducts when activated by the UV-A light.[2]

An advanced search of PubMed was subsequently conducted using the keywords, "Mycosis Fungoides" and "PUVA" generating 47 results. Results were further filtered down by analyzing every title and abstract to discern which papers would be most relevant to the clinical question, One of the relevant articles was a prospective cohort study by Sanchez et al., which compared patients on maintenance therapy with no follow up therapy.[3] The study followed 40 patients for 5 years after their diagnosis of MF, which showed no statistically significant difference in recurrence rate between the two groups. The study was not used due to the nature of a cohort study design, which is not the most ideal design for a rare disease such as MF.

The Querfeld study from 2005 was a retrospective cohort analysis looking at 66 patients with MF who achieved complete remission.[4] This study was excluded due to the fact the study did not align sufficiently with the aim of the clinical question. Researchers did not standardize the PUVA dosage for all patients, leading to differing amounts of exposure per patient. Additional maintenance therapy was performed in most, but not all, patients after their cutaneous lesions were cleared.

The Lowe study from 1979 looked at 9 patients with a known diagnosis of MF.[5] This specific study was not chosen because each patient had been on trials of other treatments prior to starting PUVA therapy, which may have skewed the outcomes. Maintenance therapy was carried out as infrequently as possible in order to control the disease, which is not ideal for the posed clinical question. The paper is also fairly outdated, which led to further investigation into more recent literature.

Grandi, Delfino, and Pileri conducted a critical appraisal on a similar topic several years ago in 2017.[6] Their paper was excluded due to the nature of its analysis and the fact that the chosen paper was published after this appraisal was conducted. Researchers evaluated new guidelines instituted from the U.S. Cutaneous Lymphoma Consortium, which recommended keeping patients in complete remission on maintenance therapy until clinical relapse.[2] The aim was to determine if maintenance phase gives a significant benefit regarding relapse rate. Due to lack of randomized trials at the time, a conclusion was made that inadequate evidence existed to support the addition of a maintenance phase to the PUVA treatment regimen. Grandi et al. suggested waiting for the results of a randomized clinical trial, which eventually was published in 2019, and became the featured article in this clinical appraisal.

A 2019 study conducted by Veiyra-Garcia, et al. was chosen for critical appraisal.[7] This is the first prospective randomized clinical trial investigating the efficacy of low-dose, low-frequency oral PUVA for maintenance. Patients who were given maintenance therapy

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were shown to have prolonged disease-free remission. The study was selected because of how recent it was published and its relevancy to the clinical question. Since the results of this RCT is the first of its kind, it adds new insight to the discussion of maintenance therapy in patients with early stage MF. Using the Strength of Recommendation Taxonomy (SORT) criteria, The Grade of Recommendation for this topic is B—limited quality, consistent studies.

Critical Appraisal

The study by Veiyra-Garcia, et al.[7] is a prospective randomized clinical trial that studied patients with early stage (IA to IIA) mycosis fungoides in Austria. According to the Strength of Recommendation Taxonomy (SORT) criteria, this study would be classified as a Level 2 study due to the fact it is considered a low-quality clinical trial, as it did not have optimal power.[8] Participants were treated with 8-methylpsoralen followed by UV-A exposure twice weekly for 12 to 24 weeks until they demonstrated a complete clinical response. The efficacy of the treatment was measured using a modified severity-weighted assessment tool (mSWAT) score, which demonstrated complete clinical response when decreased to zero and subsequently confirmed by negative biopsy results.[9]

Patients with a complete response were then randomly assigned to receive one of two treatment options; arm A received PUVA maintenance therapy for 9 months, while arm B received no maintenance therapy. It should also be mentioned that any patients that achieved only partial response to the induction therapy were not subject to randomization but were switched to an alternative therapeutic regimen. The separation of partial response patients effectively removed the chance for indication bias by dissociating complete clinical response patients from those who might have had more refractory disease. Twenty-eight total patients were assessed for eligibility, but only 19 participants met the criteria for randomization after induction therapy. A strength of this study is the randomization process; however, it was not blinded. A non-blinded study leads to a higher risk of procedure bias or observer-expectancy bias. These issues could be ameliorated in future RCT's if researchers devised a way to create a placebo for PUVA treatment. This study adequately minimized the effects of these biases by implementing a standardized method of measuring complete clinical response and relapse in patients with mSWAT and objective biopsy results.

Eligible patients were required to have early stage MF, which included only stage IA-IIA and were between the ages of 18 and 85. Patients were excluded if they had any severe cardiac insufficiency or other serious illness/infection; if they were pregnant, or if they had received any PUVA within 3 months before screening. Patients with known diagnosis of a photosensitive disease, such as systemic lupus erythematosus, were also excluded from the study.

Analysis of disease-free interval used a Kaplan-Meier analysis and log-rank test with an intention-to-treat analysis format. The threshold for statistical significance was set to $p<0.05$. For all participants, the mean percentages of body surface area involved and mSWAT scores were comparable at baseline. This was a strength of this study. Patients in the treatment group received the same cumulative dose of low-dose, low-frequency PUVA which standardized the treatment. After the first year, only 13% of patients with no maintenance therapy remained in remission, while 64% of patients in the maintenance group were found to be in remission. The median duration of disease-free remission for the treatment arm was 15 months. In comparison, the control group had a median duration of disease-free remission of 4 months ($p = 0.02$). The hazard ratio for recurrence of disease was 3.25 (95% CI, 1.14-9.29), when comparing maintenance therapy with no maintenance. The results of this 2019 study demonstrate that maintenance therapy with PUVA significantly extends the duration of disease-free remission rates in patients with mycosis fungoides. Another strength of this study was the finding that maintenance therapy not only had beneficial effects on recurrence rates, but also that the PUVA induction maintenance regimen was safe and well-tolerated. There were only very minor adverse effects in a few cases, such as nausea, vomiting, and itching. This conclusion was further supported by Youssef et al. in 2016, which demonstrated that therapeutic doses of PUVA are relatively safe in dark skinned individuals.[10]

The study was conducted in several cities across Austria, which does not accurately represent the demographics of the United States. The mean age of patients in the study was 61, which is older than our patient as well. Additionally, 70% of participants were male. According to a 2016 study by Teras et al., mycosis fungoides is more common among black individuals compared with white people, with an incidence rate ratio of 1.78.[11] Weinstock and Horm described the incidence and epidemiology of MF in the United States, which found that Detroit had the highest number of confirmed cases of MF in the country.[12] Ms. Johnson represents a demographic with a very high incidence of disease, and the Veiyra-Garcia paper may have some shortcomings with accurate

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representation in this respect. Future studies in the realm of this topic should include a patient population with a more similar demographic to the United States, and more specifically the cities that report the highest incidence of disease.

The therapeutic maneuver in this study is completely feasible for a great majority of practices, which makes the study very clinically relevant. The main limitation of the study is the small sample size. In addition, there was unequal distribution of patients in differing stages of disease randomized between the treatment arms. This shortcoming could be improved via the utilization of a propensity score matching model in future studies with a larger number of subjects. The study also failed to represent their data in reference to number needed to treat (NNT) or number needed to harm (NNH), with regards to maintenance dosing of PUVA; thus, effect size is difficult to assess.

Clinical Application

In the case of Ms. Johnson, a 47-year-old African American female, with a past medical history MF, a course of maintenance PUVA therapy may be beneficial in the long run, and we were able to recommend this to her on the strength of this evidence. The Veiyra-Garcia et al. paper is applicable to our patient because it includes a range of ages including her own, and she would fit all the inclusion criteria for the study. There was a statistically significant improvement in disease-free remission rates in patients who were subject to a maintenance therapy regimen consisting of low-dose, low-frequency PUVA, compared to patients who were subjected to induction therapy alone. A point of consideration is the difference in the white European demographic studied compared to that of Ms. Johnson in an urban environment where she resides. Additional consideration should be implemented when treating patients of color or patients with a significant family history of skin cancer, as well. This was the first RCT of its kind on this area of research, which paves the way for further research and clinical trials in the future. Therefore, the patient should be informed of the uncertainty that comes with management of this nature. Given her stated goals of prioritizing disease-free remission in order to be around her family for a long time, this evidence for the treatment was enough that she chose to pursue the maintenance treatment.

Another issue to address is the socioeconomic constraints of Ms. Johnson's situation. There were some clear challenges as far as remediating access to care, however many resources have been put in place to ensure that the best care can be provided. In some places, there are programs that assist community members with transportation as well as bus vouchers and Uber vouchers, which unfortunately, we did not have in place. We did have an expansion of clinic hours to include appointment slots before and after normal business hours, in order to accommodate the working patient who may not be able to come in during the day or patients that must work around their childcare schedules. Ms. Johnson explained that she was grateful that the physicians did not hastily change treatment plan options due to her socioeconomic status; although this is sometimes needed, in her case the team was able to work with her in order to effectively overcome hurdles to care. Based on Ms. Johnson's clinical history and success with treatment thus far, continuing with maintenance therapy is a very promising option for her moving forward with regards to safety and disease-free remission, and over at least the next two weeks during which I followed up with her, she was able to make the appointments.

New Knowledge Related to Clinical Decision Science

Social determinants of care should always be addressed before proceeding with treatment plans; it is futile to suggest a certain regimen base on empiric evidence if the patient themselves do not have the means to successfully follow the treatment course. In Ms. Johnson's case, the recommended treatment plan based of the literature was posing some socioeconomic issues. It is a lot to ask of any patient to be able to get to the clinic several times per week for treatment and becomes more difficult with uncertain access to transportation. This is something that physicians should always keep in mind while making clinical decisions and contemplating the treatment ladder. However, it is also the physician's duty to evaluate if proposed treatments offer benefits which are worth the costs, especially when the costs are not simply material, as in transportation costs, but also play out in the raising of other health risks, as with Ms. Johnson's concern for UV exposure given her family history of skin cancer. This careful evaluation of the evidence, especially when physician recommendations differ from institute to institute, provides the best opportunity for presenting enough information to the patient for them to make the best decision for themself. Clinical Decision Science forces

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doctors to ponder what might seem imponderables given our training and cultural sense of "autonomy" of patients. Whose responsibility is it to weight the harms and benefits? How do doctors help patients take concrete unidimensional evidence and integrate it into a complex life decision?

Ms. Johnson's provider was able to come up with ways to mitigate the health disparities and provide resources that fit in to the patient's social context in order to continue providing what he believed to be the best treatment option for her clinical situation which was in line with her treatment goals. In certain situations where the treatment plan is not feasible due to socioeconomic constraints and all options have been exhausted or not compatible with their other priorities, it is the physician's duty to come up with a secondary plan that works well in conjunction with the patient.

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