Skin-Directed Therapies in Cutaneous T-Cell Lymphoma

Cuong V. Nguyen, MD, Kimberly A. Bohjanen, MD*

KEYWORDS

• Skin-directed therapy • T cell • Lymphoma • Cancer • Mycosis fungoides

KEY POINTS

- Not all patients with early stage cutaneous T-cell lymphoma (CTCL) require treatment.
- Topical therapies are effective in treatment and management of early stage CTCL and as adjuvant treatment with systemic therapy for more aggressive disease.
- Topical therapies have been most extensively studied for use in mycosis fungoides. Further studies are needed to evaluate their efficacy in other forms of CTCL.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are an uncommon group of cutaneous lymphoproliferative disorders, characterized by skin infiltration with malignant mature T cells. Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), are the most common types of CTCL. Given their prevalence, most topical therapies for CTCL are primarily those used, and whose clinical efficacy has been studied, in MF/SS. These therapeutic options are numerous and varied, with treatment often based on physician experience, patient preference, and/or prognostic factors (ie, staging, histology).[1] The National Comprehensive Cancer Network (NCCN) guidelines on MF/SS provide an overall framework for treatment, but, with so many treatment alternatives, determination of regimen efficacy and timing of regimen transitions can be difficult. In 2011, the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Taskforce released a consensus statement detailing the end points and response criteria of therapy for MF/SS.[2,3] The goal of this statement was to provide a standardized method to evaluate treatment efficacy and allow more consistent research protocols. This article provides a uniform resource for choosing topical therapies for MF/SS. It summarizes the currently available skin-directed therapies for MF/SS and reviews the response rates using the Cutaneous Lymphoma Taskforce consensus statement.

TOPICAL THERAPIES

At present, there is no widely acknowledged cure for MF/SS, with death from disease ranging from 10% to 15%,[4] to up to 43%.[1] However, these adverse survival outcomes primarily apply to those patients with MF with more advanced disease. Most patients with early stage MF (stages IA, IB, and IIA) generally have favorable outcomes. Research studies in stage IA patients showed no difference in survival in those undergoing treatment compared with age-matched and sex-matched controls,[4,5] whereas patients with stage IB and IIA had an increased relative risk of 2.2.[1,6] The overall goal of therapy for MF/SS is to improve quality of life (ie, symptomatic relief, improve appearance) and delay or prevent disease progression. In early stage MF, there are no current data to show that more aggressive systemic

Department of Dermatology, University of Minnesota, 516 Delaware Street S.E., Mail Code 98, Phillips-Wangensteen Building, Suite 4-240, Minneapolis, MN 55455, USA
* Corresponding author.
E-mail address: Bohja003@umn.edu

Dermatol Clin 33 (2015) 683–696
http://dx.doi.org/10.1016/j.det.2015.05.004
0733-8635/15/$ – see front matter

regimens, including chemotherapy, modify overall survival, and they may be associated with greater morbidity and complications.[7] Thus, treatment of early stage MF tends to focus first on skin-directed therapy (SDT).

Emollients

Emollients have long been studied in the repair of compromised skin barrier.[8] Inflammatory skin conditions, like MF/SS, lead to disruption of the skin barrier, and often result in dry, scaly skin secondary to transepidermal water loss (TEWL). Emollients, or moisturizers, contain occlusive properties that prevent TEWL, and/or humectants that help to absorb water from the surrounding environment, increasing the water-holding capacity of the stratum corneum.[8,9] The most common of these humectants is glycerin, which has been shown to decrease corneocyte loss from the superficial epidermis, and alter the lipid barrier to decrease TEWL.[10,11]

To control symptoms of pruritus or scale, the use of simple emollients can be helpful.

At our site, we recommend application of emollients twice daily in the form of a cream. Although ointments are more occlusive and better moisturizers, patient compliance is often an issue given the greasy quality. In addition, the first and only randomized, placebo-controlled trial of topical emollient therapy for MF only evaluated the use of a cream emollient. This study showed that 24% of 46 patients with patch-stage or plaque-stage MF receiving a placebo of simple emollient cream achieved a partial response (PR).[12] Regardless, this high placebo response suggests an important adjunctive role for simple emollients in the treatment of MF.

Corticosteroids

Topical corticosteroids function through the binding and activation of intracytoplasmic glucocorticoid receptors. In a broad sense, they act through both antiinflammatory and antiproliferative mechanisms. They seem to affect nearly every stage of the inflammatory response. By stabilizing the cell and lysosomal membranes, they inhibit phagocytosis, and decrease monocytic and lymphocytic activity. They decrease chemical mediators such as interleukin (IL)-1, IL-2, interferon-gamma, tumor necrosis factor, and granulocyte-monocyte colony–stimulating factor.[13] Topical corticosteroids further lead to a reduction in mitotic activity and cause apoptosis of malignant cells.[14] They also reduce epidermal thickness, dermal water content, and collagen and elastic fiber production, which explains their common cutaneous side effects (further discussed later).[13]

The pharmacokinetics of topical corticosteroids are complex and depend on several factors, including structure and concentration of the drug, the vehicle, and the condition of the skin on which it is being applied. In addition, the skin can act as a reservoir for the applied drug, allowing for storage for 2 to 14 days in nonoccluded and occluded skin, respectively.[14,15] With so many disparate variables, it is often difficult to assess the pharmacokinetics and pharmacodynamics of topical corticosteroids, and their efficacy is instead assessed by means of their potency as measured through the Stoughton vasoconstriction assay.[13]

Although topical corticosteroids have been used since the 1960s for treatment of MF,[16,17] evidence for their use is still scarce. The largest prospective study to date on topical corticosteroid use in MF is that of Zackheim and colleagues.[18] Seventy-nine patients with skin stage T1 and T2 MF were treated (all of the T1 patients and 68% of the T2 patients) with class 1 topical steroids. Of the 79 patients, 94% of T1 and 82% of T2 patients showed at least a PR to treatment. A complete response (CR) was seen in 63% of T1 and 25% of T2 patients. Once therapy was stopped, only 37% of T1 and 18% of T2 patients retained complete remission. In a 2003 follow-up report, Zackheim[19] noted continued rates of PR to CR in more than 200 cases ranging from 80% to 90% in T1 and T2 patients, respectively. Lower strength topical steroids, such as low-strength to midstrength concentrations of fluocinolone acetonide 0.025% to 0.1% creams, have also been helpful, with response rates of 67% to 89%,[16,17] and can provide symptomatic relief of scale and pruritus.[20] However, for scale and pruritus, patients were treated either under occlusion with saran wrap or with wet wraps: these can be time consuming and burdensome processes for patients when used long term.

Common cutaneous side effects of topical corticosteroids include atrophy, striae, purpura, hypopigmentation, telangiectasias, acne or folliculitis, and perioral dermatitis.[13,21] Other than striae, which are permanent, most of these side effects, tend to resolve over 1 to 4 weeks with cessation of the drug.[13] In addition, allergic contact dermatitis may occur and Cushing syndrome, hyperglycemia, and unmasking of latent diabetes mellitus have been reported from systemic absorption of topical corticosteroids. After 2 weeks of continued use, almost 20% of patients using topical clobetasol for psoriasis had hypothalamus-pituitary-adrenal (HPA) axis suppression as defined by a serum cortisol level of 18 μg/dL or less 30 minutes after cosyntropin stimulation.[22] Recovery of HPA axis function is generally prompt and complete