Managing Cutaneous T-Cell Lymphoma and Related Diseases: An Update for Clinicians

Topical Treatment of Cutaneous T-Cell–Mediated Diseases: Targeting T Cells

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Innovative Strategies for Managing Patients With Cutaneous Lymphomas

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CME RECOGNITION
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TARGET AUDIENCE
This supplement was developed for dermatologists and other clinicians who are involved in the diagnosis and treatment of patients with the cutaneous manifestations of cutaneous T-cell lymphoma and natural killer cell lymphoma.

EDUCATIONAL NEEDS
Cutaneous T-cell lymphoma (CTCL) is a group of related autoimmune diseases that share an underlying pathology—namely, a malignancy of T cells—and that usually present initially with skin lesions. However, the cause is unknown. The typical clinical course of CTCL is chronic and is characterized by slow progression; the number of years of survival depends on the stage of the disease at the time of diagnosis. Patients who present with the earliest stage of the disease—ie, stage I skin involvement—may expect long-term survival if CTCL is treated early, and topical therapy often is effective when begun at this stage.

For these reasons, dermatologists must be familiar with the diagnosis of CTCL and with effective treatment options for patients at all stages of the disease. These options include oral therapy with bexarotene capsules and a novel topical therapy, bexarotene gel 1%, which has been approved by the US Food and Drug Administration for the treatment of cutaneous manifestations of CTCL. Bexarotene also is being studied in other cutaneous diseases that share with CTCL the underlying feature of abnormal T-cell activation and a pathologic increase in cytokine production. This supplement provides dermatologists with updates on both research and practical clinical management.

LEARNING OBJECTIVES
By reading and studying this supplement, participants should be able to:

• Discuss the classification and staging of cutaneous T-cell lymphoma and natural killer cell lymphoma, and state the prognosis associated with each stage.

• List and describe the skin-directed and systemic treatment options that are appropriate for each stage and cutaneous manifestation of cutaneous T-cell lymphoma.

• Discuss the algorithm for treatment of mycosis fungoides and Sézary syndrome described by John A. Zic, MD.

• Describe the clinical studies of bexarotene and explain the role of bexarotene topical gel and oral formulation (capsules) in the treatment of cutaneous T-cell lymphoma.

FACULTY AND UNAPPROVED USE DISCLOSURES
Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. The faculty must also disclose any discussion of investigational or unlabeled uses of products.

Dr Demierre has received funding from Ligand Pharmaceuticals Inc. for Mycosis Fungoides Foundation Surveys. She is also a consultant to and has a Speaker Agreement with Ligand. She discusses the investigational use of bexarotene gel 1% in the treatment of hand dermatitis, psoriasis, and alopecia areata.

Dr Zic has received funding for a photopheresis study from Therakos, Inc., and is on the Speakers’ Boards at Ligand and Therakos. He is also a consultant to Ligand. Dr Zic discusses the investigational combined use of gemcitabine and pegylated liposomal doxorubicin for the treatment of advanced cutaneous T-cell lymphoma.
Several skin disorders are characterized by inflammation. Although these diseases are very different, they share a central pathogenic mechanism: T-cell activation, which results in cytokine release, recruitment, and proliferation and also has an impact on keratinocytes.

This article focuses on the elements of T-cell activation and the therapeutic mechanisms involved in mycosis fungoides, inflammatory dermatoses (such as hand dermatitis), psoriasis, and alopecia areata. Also discussed are the mechanisms of action of retinoids that have been identified, as well as the results of clinical studies of bexarotene gel and the potential for the future use of bexarotene.

Pathogenesis of Inflammatory Skin Diseases: The Role of T Cells and Cytokines

An appreciation of the cytokine-mediated disease process is important in understanding how targeting cytokine dysregulation is a useful approach to treatment of cutaneous T-cell lymphoma (CTCL) and some other inflammatory skin diseases.

As malignant T cells proliferate and CTCL progresses, a shift occurs in the cytokine pattern, changing from T-helper type 1 (T\(_{H1}\)) to T\(_{H2}\) predominance. T\(_{H1}\) cells are associated with cell-mediated immunity and the delayed hypersensitivity reaction, whereas T\(_{H2}\) cells are associated with antibody formation and the allergic response. In the earliest stages of mycosis fungoides (the most common type of CTCL, which primarily affects the skin), T cells are recruited first in the epidermis and then in the dermis, gradually involving T\(_{H2}\) cells.

With worsening disease, production of T\(_{H2}\) cytokines increases, including interleukin (IL)-4 (associated with increased levels of immunoglobulin E and a decrease in T\(_{H1}\) cells), IL-5 (associated with eosinophilia), and IL-10 (which contributes to the decrease in T\(_{H1}\) and dendritic cell activity and reduces cell-mediated immunity).\(^1\)

Cytokine dysregulation also is central to the pathogenesis of chronic inflammatory dermatoses such as severe hand dermatitis. Alopecia areata is an autoimmune disease, mediated by T-helper lymphocytes with a T\(_{H1}\) cytokine profile, in which T cells target anagen hair follicles. In psoriasis, the progression of disease is marked by initial activation of T-helper lymphocytes, the migration of these cells into the skin, and cytokine release that results in abnormal proliferation and differentiation of keratinocytes.

The Role of Rexinoids in Treating Immune Dysregulation

Rexinoids represent the most recent generation of retinoids. Both retinoids

![FIGURE 1: Pathways of Retinoid Activity](image)

COX = cyclooxygenase; CTCL = cutaneous T-cell lymphoma; ICAM = intercellular adhesion molecule; NF-\(\kappa\)B = nuclear factor kappa B; NHR = nuclear hormone receptor; PPAR = peroxisome proliferator-activated receptor; RAR = retinoic acid receptor; RXR = retinoid X receptor; T\(_{H2}\) = T-helper type 2 cell; VCAM = vascular cell adhesion molecule.

and rexinoids are gene-regulating molecules. They are hormonelike molecules that, like steroid hormones, bind to receptors in the nucleus of the target cell, acting as “keys” to unlock gene activity. Retinoids (eg, tretinoin) and rexinoids (eg, bexarotene) share two main features: both interact with nuclear receptors that control genes to decrease cell proliferation and increase cell differentiation. Unlike retinoids, however, rexinoids also may affect the genes involved in apoptosis and inflammation in targeted cells such as T cells.

Rexinoids downregulate the genes that trigger inflammation by modulating signaling pathways controlled by nuclear receptors. Rexinoids may be able to inhibit the activation of inflammatory genes, resulting in the inhibition of cytokine release from immune cells. All four of the dermatologic diseases mentioned above have inflammatory components that are potentially responsive to rexinoids or retinoids.

Recent research has indicated that rexinoid molecules alone also can interact with other hormonal receptors, including the peroxisome proliferator-activated receptor (PPAR)-γ, which may be active in the pathogenesis of diabetes and psoriasis (Figure 1 on page 4). Bexarotene, applied topically, targets the PPAR-γ receptor and also directly targets some of the inflammatory mediators that are overexpressed in mycosis fungoides, chronic dermatitis, psoriasis, and alopecia areata. In CTCL, it is postulated that one of the final important mechanisms of rexinoids is apoptosis of the autoreactive malignant T cells.

Clinical Studies of Bexarotene
Topical bexarotene gel 1% currently is approved by the US Food and Drug Administration (FDA) for the treatment of the skin manifestations of CTCL. This agent also is being studied for efficacy and safety in other disorders, including severe hand dermatitis (phase I and II clinical trials), psoriasis (phase II trials), and alopecia areata (phase II randomized study).

Skin Manifestations of Early CTCL
FDA approval of bexarotene gel for skin manifestations of CTCL was granted on the basis of a multinational, open-label phase III study. The entry criteria for the study included refractory or persistent early-stage (stage IA to IIA) CTCL. The subjects who participated in the study had failed prior therapy with two or more standard treatments, including topical and systemic modalities and phototherapy.

The primary end point was overall complete and partial response as rated on a physician’s global assessment of clinical condition or on the Composite Assessment of Lesion Disease Severity (the higher of the two ratings was considered to be the end result for efficacy for each patient). The overall response rate was 54%. The intended treatment time was 16 weeks, but patients had the option to continue beyond this time. The median time to good response in this study was 12 weeks (Figure 2).
The most common adverse events that were seen in the study population were mild to moderate irritant dermatitis, pruritus, pain (described by the investigators as primarily burning at the site of application), and skin disorders such as irritation, excoriation, and new lesions. These adverse events were considered to be possibly related to the study medication. At least one episode of irritation was reported in 64% of patients, but most such episodes were mild to moderate.

Heald and coworkers\(^2\) concluded that bexarotene gel was generally well tolerated and substantially effective for the treatment of refractory or persistent early-stage CTCL.

Severe Hand Dermatitis
In a phase II study of patients with hand dermatitis, Hanifin and colleagues\(^3\) compared treatment with bexarotene monotherapy, bexarotene plus mometasone furoate, and bexarotene plus hydrocortisone in 55 patients with severe irritant, atopic, and dyshidrotic hand dermatitis (individuals with allergic dermatitis were excluded from the study). The study population was divided in a 2:1:1 ratio (ie, bexarotene alone, n=28; bexarotene plus mometasone furoate, n=13; bexarotene plus hydrocortisone, n=14).

All of the patients in the groups who used bexarotene in combination applied the corticosteroid twice daily. In all three arms of the study, bexarotene gel was applied in an escalating dosage, beginning every other day, then to once daily, twice daily, and three times daily.

The primary end point was at least 90% skin clearance, which was achieved by 39% (n=11) of patients who received bexarotene monotherapy, 46% (n=6) of those in the bexarotene/mometasone furoate group, and 21% (n=3) of subjects in the bexarotene/hydrocortisone group. The secondary end point was at least 50% clearance, which was achieved by 79% (n=22) of patients in the bexarotene monotherapy group, compared with 77% (n=10) of the bexarotene/mometasone furoate group and 50% (n=7) of the bexarotene/hydrocortisone group.

A subgroup analysis of response to treatment according to types of dermatitis showed 90% or greater skin clearance in 26%, 61%, and 17% of patients with atopic, irritant, and dyshidrotic disease, respectively. Clearance of 50% or greater was seen in 71%, 83%, and 33% of those with atopic, irritant, and dyshidrotic dermatitis, respectively.

One important observation from this study is that in the entire study population as well as in the subgroups with atopic, irritant, and dyshidrotic disease, the addition of mometasone furoate or hydrocortisone to bexarotene gel made no significant difference in clinical response. The addition of mometasone furoate appeared to improve the amount of skin clearance achieved only in the atopic subpopulation.

Psoriasis
A small, open-label pilot study of bexarotene gel 1% in psoriasis was conducted by Breneman and coworkers in Cincinnati. The study involved 24 patients with mild to moderate plaque psoriasis covering 15% or less of body surface area. The bexarotene regimen began with applications every other day, then escalated to daily, twice daily, and, in some patients, four times daily. The intended treatment duration was 16 weeks, and patients who responded continued therapy for another 8 weeks. For sensitive skin areas (the face, scalp, axillae, and groin), patients could choose to not treat them, treat them with hydrocortisone cream, or treat them with bexarotene gel at any tolerated frequency.

The results of this study currently are under review for publication. Responses of at least 50% global improvement in disease were observed in 63% of patients, and 24% achieved a clearing of 90% or greater. Responses were maintained off-treatment for at least an additional 8 weeks in 40% of responders. As with the study of bexarotene in CTCL, the median time to response is about 12 weeks and the frequency of application seems to have an effect on the degree of response to the medication. The side effects were mild to moderate application-site complaints, with irritation being the most common.

Alopecia Areata
The treatment of alopecia areata is rarely successful with the currently available treatments, but the strategy of targeting T-cell activation and inhibition of cytokine release seems to offer hope for clinical improvement. In an ongoing phase II study of a small group of patients with alopecia by Duvic and colleagues\(^4\), 42 patients applied bexarotene gel 1% to half of the scalp once daily for 2 weeks, then twice daily for an additional 22 weeks. Preliminary data on 21 patients who have completed the study show that 4 of 21 had greater than 50% hair regrowth on the treated side of the scalp and another 4 had minor hair regrowth. The most common adverse event reported has been irritation.

Bexarotene-Related Irritation
In all of the studies discussed here, topical bexarotene was irritating in approximately one third to one half of subjects. The preliminary data from the alopecia study by Duvic and colleagues\(^4\) and the psoriasis study by Breneman and coworkers, as well as prior studies in CTCL, indicate that irritation seems to be the most common side effect. In these studies, irritation is typically mild to moderate in severity.

In a blinded, placebo-controlled irritation patch test trial in normal volunteers, the irritation potential of bexarotene gel was similar to that seen with adapalene gel and two to three times less than what was observed with tretinoin gel. In the published study in
The treatment of cutaneous T-cell lymphoma (CTCL) can take any of a number of pathways, depending primarily on the stage of the patient's disease and on the response to initial therapies. This article discusses a practical, algorithmic approach to individualizing treatment choices and addresses one of the newer options, bexarotene capsules.

Classification and Staging of CTCL
Jean Louis Alibert, a pioneer in dermatology in France, is credited with describing the first case of mycosis fungoides in the medical literature in a paper published in 1806.

Mycosis fungoides is still the most common variant of CTCL, but a number of other types of CTCL and natural killer cell lymphomas have been identified. The World Health Organization and the European Organization for Research on the Treatment of Cancer published an updated classification system for these lymphomas in May 2005 (Table 1).1

Mycosis fungoides is staged according to degrees of involvement of skin and lymph nodes and whether visceral involvement is present (Table 2 on page 8). Skin involvement is classified in four stages: T1, limited patches or plaques—less than 10% of body surface area (BSA); T2, generalized patches and plaques affecting 10% or more of BSA; T3, skin tumors; T4, generalized erythroderma. The prognosis is worst for patients with stages T3 and T4 skin disease and progressively worse as the disease advances from stage T1 to T2, then to T3 skin stages (Table 3 on page 8).2

Therapeutic Options for CTCL
The list of treatment options for CTCL is extensive; the algorithm shown in Figure 1 on page 9 provides a schematic view of the roles of both skin-directed and systemic treatments that may be considered according to the staging of the disease.

The topical treatment options bexarotene gel, corticosteroids, and nitrogen mustard play important roles in the management of early-stage disease. Phototherapy—including narrowband ultraviolet B light and psoralen plus ultraviolet A light (PUVA)—can be effective in managing certain cutaneous manifestations of CTCL. These treatments work by inducing apoptosis in lymphocytes. Other effective radiation strategies are total skin electron beam or localized electron beam therapy in patients who have failed one or more standard topical therapies or in those with cutaneous tumors.

Oral bexarotene can be used to manage early-stage patients in whom other therapies have failed, but the primary role for such systemic treatment is in patients with aggressive, later-stage disease. Other options for such patients are the fusion toxin denileukin difitox, interferon, photopheresis (primarily for patients with erythroderma and leukemic involvement—ie, Sézary syndrome), chemotherapy, and allogeneic bone marrow transplantation.

Among the skin-directed therapies, topical corticosteroids have been for many years a mainstay of treatment for the earliest stages of mycosis fungoides, and these agents still are excellent choices. Topical nitrogen mustard, de-
developed and introduced in the 1940s, also is still a viable option. Carmustine and, most recently introduced, bexarotene gel 1% also are effective in the early stages of CTCL. In her article on page 4, Dr Demierre reviews in more detail the mechanisms of action and the clinical trials involving topical bexarotene in several skin diseases that have T-cell dysregulation in common.

**Table 2: Staging of Cutaneous T-Cell Lymphoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin (T)</th>
<th>Node infiltration/Presence of adenopathy (N)</th>
<th>Visceral involvement (M)</th>
<th>Extent of lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1</td>
<td>N0/−</td>
<td>M0</td>
<td>Patches or plaques &lt;10% BSA</td>
</tr>
<tr>
<td>Ib</td>
<td>T2</td>
<td>N0/−</td>
<td>M0</td>
<td>Patches or plaques ≥10% BSA</td>
</tr>
<tr>
<td>Ila</td>
<td>T1-2</td>
<td>N1/+</td>
<td>M0</td>
<td>With palpable, histologically negative or dermatotropic nodes</td>
</tr>
<tr>
<td>Iib</td>
<td>T3</td>
<td>N0-1/+ or −</td>
<td>M0</td>
<td>Cutaneous tumors present</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0-2/+ or −</td>
<td>M0</td>
<td>Erythroderma without lymph node involvement</td>
</tr>
<tr>
<td>IVa</td>
<td>T1-4</td>
<td>N3-4/+ or −</td>
<td>M0</td>
<td>Nodes are involved</td>
</tr>
<tr>
<td>IVb</td>
<td>T1-4</td>
<td>N0-4/+ or −</td>
<td>M1</td>
<td>Visceral disease present</td>
</tr>
</tbody>
</table>

BSA: Body surface area; SS: Sézary syndrome

**Skin involvement**: T1 = no lesions; T2 = patches and plaques, <10% BSA; T3 = patches and plaques, ≥10% BSA; T4 = generalized erythroderma

**Lymphoma infiltration into nodes**: N0 = none; N1 = dermatopathic; N2 = occasional atypical cells; N3 = clusters of atypical cells; N4 = complete effacement

**Adenopathy**: + = present; − = not present

**Visceral involvement**: M0 = no evidence of visceral disease; M1 = visceral disease present


**Table 3: Cutaneous T-Cell Lymphoma Prognostic Groups**

**Low-risk group: survival ~12 years**

TNM stages Ia, Ib, Ila

**Intermediate-risk group: survival ~2–3 years**

TNM stages Iib, II, IVa with grade LN3 lymph node histopathology

**High-risk group: survival ~ < 2 years**

TNM stages IVb, IVa with grade LN4 lymph node histopathology

**Source**: Foss and Sauville.² Used with permission.

**Systemic Retinoids: An Overview of Mechanism of Action**

Several retinoids are available to dermatologists for the treatment of a number of diseases, including CTCL: isotretinoin, acitretin, and bexarotene. Acitretin and, possibly, isotretinoin bind to retinoic acid receptors (RAR). Bexarotene is a retinoid X receptor (RXR) ligand. The RXR binds to a “partner receptor” in order to effect the regulation of various gene networks. The RXR partners include RAR, peroxisome proliferator-activated receptor (PPAR)-α and -γ, liver X receptor, nerve growth factor induced-β, farnesoic X receptor, and steroid X receptor, among others. These bindings result in actions on gene networks that are responsible for a number of functions, including cell cycle control, metabolism, differentiation, and apoptosis.

This interaction also results in side effects. For example, oral bexarotene can cause hyperlipidemia, possibly an adipogenic result of RXR co-binding with PPAR-γ. This topic will be addressed below in more detail.

The use of bexarotene to treat CTCL is based on several studies.³-⁵ The pivotal trial was published by Duvic and colleagues⁵ and involved 94 patients with both early- and late-stage CTCL. Many of the subjects had failed standard therapies before entering the trial. The overall response rate was 48%, with patients in the early stages of the disease having higher response rates (54%) than those who had later-stage CTCL (45%). The relapse rate was about 28% among patients who had at least a partial response to the drug; the median time to relapse was 43 weeks. To put these data into perspective, chemotherapeutic agents are quite effective, but relapses within 6 to 12 weeks are common.

**Managing Side Effects of Bexarotene**

The adverse effect profile for bexarotene is quite similar to that for other systemic retinoids. The most common is hyperlipidemia, which occurs to at least some degree in almost all patients. Central hypothyroidism also can be seen in a majority of patients on bexarotene and may require thyroid supplementation. Bexarotene does not cause profound immunosuppression, but some decrease may be seen in a patient’s white blood cell count; however, there have been no reports of a se-
rious increase in infection rates among patients taking bexarotene.

Prevention and management of these side effects (Figure 2 on page 10) must begin at the onset of bexarotene therapy and should include all of the following: (1) baseline fasting lipid panel, liver function tests, complete blood count, thyroid-stimulating hormone (TSH) test, total or free thyroxine (T₄) test, and, when appropriate, pregnancy test; (2) a review of medical and medication history; (3) counseling regarding prophylactic lifestyle/diet modifications, such as exercise, eating small meals low in calories, sugar, and saturated fat, and limiting alcohol consumption; and (4) prophylactic ω-3 fatty acid supplementation.

Hyperlipidemia
The main concern with hyperlipidemia, particularly hypertriglyceridemia, is the development of pancreatitis. To help keep triglyceride levels within the normal range, patients should be counseled as in #3 above. Initiation of a statin medication along with bexarotene is an option, but prophylactic ω-3 fatty acid supplementation may work better to control hypertriglyceridemia, particularly in patients who are obese and/or have diabetes.

Most patients require medication to manage lipid levels. One antilipidemic agent that should be avoided is gemfibrozil, which seems to cause an increase in bexarotene blood levels.

Central Hypothyroidism
Central hypothyroidism—that is, decreased levels of TSH and free T₄—affects about two thirds of patients taking bexarotene. TSH levels remain suppressed as long as a patient is taking bexarotene, but free T₄ levels can be managed by levothyroxine treatment, beginning with a relatively low dosage and slowly increasing the dosage every 4 to 6 weeks. Free T₄ levels should be checked once every other week for the first month of bexarotene therapy, then every 1 to 2 months thereafter.

The goal is to maintain a free T₄ level at the patient’s baseline value.

Applying the Algorithm
Referring to the algorithm shown in Figure 1, the graphic representation suggests that sequential monotherapy is recommended. However, this is not the case. Most patients with CTCL are managed with combinations of therapies, and, for example, data support combining interferon and PUVA, and bexarotene and other rexinoids with PUVA for earlier-stage patients. Patients with tumor-stage disease often are first treated with localized or total skin electron beam radiation therapy followed by topical nitrogen mustard or bexarotene capsules to prevent relapse. For patients with Sézary syndrome, photopheresis appears to help in many cases, and more refractory patients seem to respond well to the addition of interferon, with or without oral bexarotene.

Chemotherapy should be reserved for the most refractory cases and should be put off for as long as possible. An exception may be gemcitabine and pegylated liposomal doxorubicin; some data are now available that suggest that this combination may be helpful in some patients with more advanced CTCL.

For patients who have failed multiple therapies, allogeneic peripheral stem cell transplantation is an option to consider. A few case reports in the literature show that this modality may be helpful.

Sézary syndrome, the second most common type of CTCL, is characterized by erythroderma and the appearance of cerebriform T cells (Sézary cells) in the peripheral blood. Sézary syndrome carries a poor prognosis, with median survival measured in just months—usual-
### FIGURE 2: Managing Hyperlipidemia and Hypothyroidism During Bexarotene Therapy

#### LIPID ABNORMALITIES

**Baseline**
- Laboratory assessments: CK, FLL, LFT, pregnancy test, TSH, total T4, WBC
- Review medical and medication history
- Counsel patient regarding lifestyle/diet modifications: exercise; small meals low in calories, sugar, and saturated fat; limited alcohol intake
- Start prophylactic 3 fatty acid supplementation

**If Baseline TG < 300 mg/dL**
- Consider starting prophylactic antilipidemic TX 1 week before starting bexarotene
- Start bexarotene at 300 mg/m2/day

**If Baseline TG > 300 mg/dL**
- Start antilipidemic TX
- Consider starting bexarotene when TG level normalizes

#### HYPOTHYROID

**Hypothyroid**
- If patient is hypothyroid at baseline or at any time during bexarotene TX:
  - Start levothyroxine at 0.025–0.05 mg/day
  - Increase levothyroxine dose by 0.025 mg as needed until T4 is normal (TSH will remain suppressed)
  - Monitor thyroid function at patient visits
  - Consider referral to endocrinologist

#### Monitor FLL and LFT Beginning At Week 1

- If at any time during therapy LFT > 3X normal and/or symptoms of myopathy or elevated CK develop:
  - Discontinue antilipidemic agent AND
  - Decrease bexarotene dosage

- If Baseline TG = 300-1000 mg/dL
  - Continue bexarotene
  - Adjust antilipidemic TX, maximizing dosage of one agent before starting another.
  - Reinforce lifestyle and diet modification counseling
  - Monitor TG at weeks 2 and 4, then monthly if stable
  - Perform LFTs at weeks 2 and 4, then every 8 weeks if stable
  - Consider referral to lipid specialist and/or nutritionist
  - If TG > 800 mg/dL, consider bexarotene dosage reduction

- If Baseline TG > 1000 mg/dL
  - Suspend bexarotene TX
  - Adjust antilipidemic TX, maximizing dosage of one agent before starting another
  - When TG < 400 mg/dL, restart bexarotene at ½ normal dosage
  - Monitor TG within 1 week and periodically thereafter

#### Continue Patient Management

- Consider adding 3 fatty acid supplementation (6–9 fish oil capsules/day with meals)
- Consider increasing long-acting niacin.
- Uncorrected hypothyroidism decreases lipid clearance and makes triglyceride levels more difficult to control.

*Note that combining antilipidemic agents increases the risk for rhabdomyolysis.

**Source:** Courtesy of Bexarotene Treatment Optimization Working Group. Used with permission.

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**Laboratory assessments:**
- CK = creatine kinase; FLL = fasting lipid level panel; LFT = liver function tests
- T4 = thyroxine; TG = triglyceride levels (fasting)
- TSH = thyroid-stimulating hormone; WBC = white blood cell count

*Choice of antilipidemic agent depends on level of dyslipidemias, current concomitant medications, age, and cardiovascular risk factors. Possible regimens include: fenofibrate, 145 mg/day OR atorvastatin, 20-40 mg/day OR simvastatin, 20-40 mg/day AND long-acting niacin, 500-1000 mg/day. Consult the current package insert of these drugs for full prescribing information.

*Consult the current package insert of this

**TG < 300 mg/dL**
- Continue bexarotene 300 mg/m2/day AND antilipidemic TX
- Monitor TG at weeks 2 and 4, then monthly if TG is stable

**TG = 300-1000 mg/dL**
- Continue bexarotene
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another.
- Reinforce lifestyle and diet modification counseling
- Monitor TG at weeks 2 and 4, then monthly if stable
- Perform LFTs at weeks 2 and 4, then every 8 weeks if stable
- Consider referral to lipid specialist and/or nutritionist
- If TG > 800 mg/dL, consider bexarotene dosage reduction

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- Suspend bexarotene TX
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another
- When TG < 400 mg/dL, restart bexarotene at ½ normal dosage
- Monitor TG within 1 week and periodically thereafter

**Consider adding 3 fatty acid supplementation (6–9 fish oil capsules/day with meals)**
- Consider increasing long-acting niacin.
- UNCROCTED hypothyroidism decreases lipid clearance and makes triglyceride levels more difficult to control.

**Source:** Courtesy of Bexarotene Treatment Optimization Working Group. Used with permission.

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*Consult the current package insert of this

**TG < 300 mg/dL**
- Continue bexarotene 300 mg/m2/day AND antilipidemic TX
- Monitor TG at weeks 2 and 4, then monthly if TG is stable

**TG = 300-1000 mg/dL**
- Continue bexarotene
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another.
- Reinforce lifestyle and diet modification counseling
- Monitor TG at weeks 2 and 4, then monthly if stable
- Perform LFTs at weeks 2 and 4, then every 8 weeks if stable
- Consider referral to lipid specialist and/or nutritionist
- If TG > 800 mg/dL, consider bexarotene dosage reduction

**TG > 1000 mg/dL**
- Suspend bexarotene TX
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another
- When TG < 400 mg/dL, restart bexarotene at ½ normal dosage
- Monitor TG within 1 week and periodically thereafter

**Consider adding 3 fatty acid supplementation (6–9 fish oil capsules/day with meals)**
- Consider increasing long-acting niacin.
- UNCROCTED hypothyroidism decreases lipid clearance and makes triglyceride levels more difficult to control.

**Source:** Courtesy of Bexarotene Treatment Optimization Working Group. Used with permission.

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**Laboratory assessments:**
- CK = creatine kinase; FLL = fasting lipid level panel; LFT = liver function tests
- T4 = thyroxine; TG = triglyceride levels (fasting)
- TSH = thyroid-stimulating hormone; WBC = white blood cell count

*Choice of antilipidemic agent depends on level of dyslipidemias, current concomitant medications, age, and cardiovascular risk factors. Possible regimens include: fenofibrate, 145 mg/day OR atorvastatin, 20-40 mg/day OR simvastatin, 20-40 mg/day AND long-acting niacin, 500-1000 mg/day. Consult the current package insert of these drugs for full prescribing information.

*Consult the current package insert of this

**TG < 300 mg/dL**
- Continue bexarotene 300 mg/m2/day AND antilipidemic TX
- Monitor TG at weeks 2 and 4, then monthly if TG is stable

**TG = 300-1000 mg/dL**
- Continue bexarotene
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another.
- Reinforce lifestyle and diet modification counseling
- Monitor TG at weeks 2 and 4, then monthly if stable
- Perform LFTs at weeks 2 and 4, then every 8 weeks if stable
- Consider referral to lipid specialist and/or nutritionist
- If TG > 800 mg/dL, consider bexarotene dosage reduction

**TG > 1000 mg/dL**
- Suspend bexarotene TX
- Adjust antilipidemic TX, maximizing dosage of one agent before starting another
- When TG < 400 mg/dL, restart bexarotene at ½ normal dosage
- Monitor TG within 1 week and periodically thereafter

**Consider adding 3 fatty acid supplementation (6–9 fish oil capsules/day with meals)**
- Consider increasing long-acting niacin.
- UNCROCTED hypothyroidism decreases lipid clearance and makes triglyceride levels more difficult to control.

**Source:** Courtesy of Bexarotene Treatment Optimization Working Group. Used with permission.
ly 20 to 36 months, and perhaps up to 40 months. As mentioned above, one approach to treatment of this syndrome is photopheresis, an apheresis procedure in which a leukopheresed fraction of blood is exposed to UVA energy and 8-methoxypsoralen. The exact mechanism of action is still debated but involves the induction of apoptosis and possibly effecting an immune response against the malignant clones.

**Conclusion**

Many skin-directed treatments are available for patients in the early stages of CTCL. These treatments are highly effective, but relapse of the disease is common. The research challenge for the future is the development of systemic therapies that offer minimal toxicity and are capable of inducing meaningful remissions. Meanwhile, the overall treatment strategy that will best serve our patients by increasing the duration and quality of their lives is to optimize the use of the least toxic therapies and to avoid the more toxic systemic agents until they are required.

**References**


**Topical Treatment of Cutaneous T-Cell–Mediated Diseases: Targeting T Cells**

*Continued from page 6*

CTCL, Heald et al.\(^2\) reported that 64% of patients experienced irritation at least once during the study. In the hand dermatitis study,\(^3\) the subjects all were patients in whom prior treatment with standard therapies—including phototherapy and topical calcineurin inhibitors—had failed and in whom irritation was mild to moderate. Interestingly, the patients in the group with irritant dermatitis had the greatest responses: 61% had clearance of 90% or greater and 83% had 50% or greater clearance of their dermatitis.

It is not yet clear—and, from such small samples, it cannot be determined—whether the degree of irritation seen in these trials can be attributed to the alcohol-based formulation or to bexarotene itself. Nevertheless, clinical experience has shown that application of bexarotene gel to normal skin can result in irritation. Thus, it probably is useful to gradually increase application of the medication to the involved skin and, to prevent exposure of normal skin, consider applying petroleum jelly to the skin surrounding the treatment site.

**Conclusion**

Bexarotene is a unique, nonimmunosuppressive, topical retinoid X receptor molecule that targets T-cell–mediated diseases. One important likely mechanism of action is the induction of apoptosis in autoreactive or malignant T cells and the modulation of inflammatory cytokines in the skin. Exploration of the exact role of bexarotene gel 1% is ongoing, but currently it is approved for the treatment of the cutaneous manifestations of early CTCL, and the results of phase II studies suggest that it may be a welcome addition to the list of treatment options for hand dermatitis, psoriasis, and alopecia areata. Both clinical and cost-effectiveness studies are warranted for the future.

**References**

Managing Cutaneous T-Cell Lymphoma and Related Diseases: An Update for Clinicians

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INSTRUCTIONS: For each question or incomplete statement, circle the most appropriate response. Six correct responses are required for credit.

1. In the earliest stages of _________, T cells are recruited first in the epidermis then in the dermis, gradually involving T-helper type 2 (Th2) cells, with a shift in the cytokine pattern, changing from Th1 to Th2 predominance.
   a. Alopecia areata  
   b. Atopic hand dermatitis  
   c. Mycosis fungoides  
   d. Pustulosis

2. Retinoids and rexinoids are classified as:
   a. Genes  
   b. Hormones  
   c. Ligands  
   d. Receptors

3. The rexinoid molecule bexarotene shares which one of the following features with retinoid molecules?
   a. Both interact with retinoic acid receptors to decrease T-cell proliferation.  
   b. Both promote apoptosis in targeted pathologic cells.  
   c. Both downregulate the genes that trigger inflammation.  
   d. Both interact with peroxisome proliferator-activated receptor-γ.

4. In the phase III clinical study of topical bexarotene gel 1% in cutaneous T-cell lymphoma (CTCL), Heald and colleagues found all of the following except:
   a. A median time to good response of 12 weeks  
   b. An overall response rate of 54%  
   c. Evidence of systemic immunosuppression  
   d. Irritation as an adverse event in 64% of patients

5. Topical treatment options for CTCL include all of the following except:
   a. Bexarotene gel  
   b. Corticosteroids  
   c. Denileukin diftitox  
   d. Nitrogen mustard

6. Among the following choices, the poorest prognosis is associated with:
   a. Stage II skin disease  
   b. Sézary syndrome  
   c. Visceral involvement  
   d. Skin tumors

7. The most common side effect associated with oral bexarotene therapy is:
   a. Central hypothyroidism  
   b. Hyperlipidemia  
   c. Immunosuppression  
   d. Leukopenia

8. The median time to relapse with chemotherapeutic agents in patients with CTCL is 6 to 12 weeks. In the pivotal trial of bexarotene by Duvic and colleagues discussed in Dr Zic's article in this supplement (page 7), the median time to relapse after oral bexarotene treatment was:
   a. 15 weeks  
   b. 23 weeks  
   c. 33 weeks  
   d. 43 weeks

EVALUATION FORM: We would appreciate your answering the following questions in order to help us plan for other activities of this type.

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   Comments:

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