The Role of Systemic Retinoids in the Treatment of Cutaneous T-Cell Lymphoma

Auris O. Huen, PharmD, MD, Ellen J. Kim, MD*

KEYWORDS

• Retinoids • Rexinoids • Bexarotene • Isotretinoin • Acitretin • Cutaneous T-cell lymphoma • Mycosis fungoides • Sézary syndrome

KEY POINTS

- Mycosis fungoides and Sézary syndrome subtypes of cutaneous T-cell lymphoma (CTCL) have a variable clinical course, ranging from indolent disease that does not alter life expectancy to aggressive, rapidly progressive disease.
- Goals of treatment, especially in patients with early-stage disease, are to induce remission with agents that have a low toxicity profile. The systemic retinoids are an important component of the treatment options for all stages of this disease because of the ease of administration and relatively low toxicity profile.
- Bexarotene is the only systemic retinoid approved by the Food and Drug Administration specifically for CTCL but does require additional medications to treat the associated hyperlipidemia and hypothyroidism during the duration of bexarotene treatment.
- Combination treatment with retinoids and other agents with activity against mycosis fungoides/Sézary syndrome appear to be well tolerated and associated with high response rates in relapsed or treatment refractory patients in small studies and series.

INTRODUCTION

Retinoids are signaling molecules that are structural and functional derivatives of vitamin A (retinol). The term collectively describes naturally occurring retinol and its metabolites, as well as synthetic analogs. Retinoid receptors are found ubiquitously in virtually all organ systems, and they regulate important functions in the body, including embryonic development, vision, immune and neural function, as well as cell proliferation, differentiation, and apoptosis.[1,2] These compounds exert their effects through control of gene expression. In the treatment of cancer, the retinoids are considered "biologic response modifiers" (BRMs) in that they are dissimilar to traditional cytotoxic chemotherapy, inducing response without immune suppression, and often augmenting the immune response.[3–5] Although there have been a number of clinical studies using retinoids for treatment of breast, ovarian, renal, head and neck, melanoma, and prostate cancers, they are most prominently used in the treatment of hematologic malignancies. In the case of acute promyelocytic leukemia, retinoids in the form of all-*trans* retinoic acid are used as first-line treatment to restore normal myeloid

Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Boulevard, Suite 330S, Philadelphia, PA 19104, USA
* Corresponding author. Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 1 Dulles Building, 3400 Spruce Street, Philadelphia, PA 19104.
E-mail address: Ellen.Kim@uphs.upenn.edu

Dermatol Clin 33 (2015) 715–729
http://dx.doi.org/10.1016/j.det.2015.05.007
0733-8635/15/$ – see front matter

differentiation to leukemic cells, inducing the formation of mature granulocytes.[6] In T-cell lymphoma cells, retinoids are thought to induce apoptosis and DNA fragmentation in affected T lymphocytes.[7,8]

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of uncommon primarily mature T-helper lymphoproliferative disorders. The most common form is mycosis fungoides (MF), which accounts for approximately 60% of all cases.[9] It typically displays indolent behavior, although disease progression to higher stages or transformation to large-cell lymphoma can occur. Sézary syndrome (SS) is a related subtype of CTCL presenting as erythroderma, with a significant population of circulating atypical T-lymphocytes and typically has a more aggressive course than MF. Patients with the earliest stages of MF do not have decreased survival due to their disease, and skin-directed therapy, such as phototherapy or topical medications, are the mainstays of treatment.[10] Additionally, treatment with BRMs, such as interferons or retinoids, also are commonly used in these patients, although systemic treatment is generally reserved for patients with MF who have failed local or skin-directed therapy or have more extensive disease.[5,10] The anecdotal use of retinoids for treatment of MF was first reported in the 1980s, both as monotherapy or in combination with chemotherapy.[3,11,12] Currently, topical and systemic retinoids are an integral part of the treatment armamentarium for CTCL. This article focuses primarily on systemic retinoids in MF and SS.

RETINOIDS AND MECHANISM OF ACTION

All retinoids have similar molecular structure, containing a benzene ring, a polyene chain, and a carboxylic end group. In the body, retinol is metabolized to all-*trans* retinoic acid and then further isomerizes to 13-*cis* retinoic acid (isotretinoin) and 9-*cis* retinoic acid in the liver.[2] Subsequently, synthetic retinoids have been derived from retinol, including mono-aromatic second-generation retinoids (eg, etretinate, acitretin) followed by polyaromatic third-generation compounds called arotenoids (eg, bexarotene).[13] More recently, alitretinoin, which is a synthetic analog of 9-*cis* retinoic acid, has been developed with efficacy in atopic dermatitis and a few reports showing effects in MF/SS.

Retinoids bind to 2 distinct families of nuclear receptors regulating gene transcription called retinoic acid receptors (RARs) and retinoic X receptors (RXRs). Each receptor is associated with 3 subtypes, α, β, and, γ, which bind to specific ligands.[1,14] These receptors are part of a larger superfamily of nuclear receptors, including thyroid hormone receptor, vitamin D3 receptor, and glucocorticoid receptor (**Table 1**).[1] Transactivation of some of these other nuclear receptors is believed to be linked to some of the side effects seen with the retinoids.[1]

Despite significant progress in elucidating the mechanism by which retinoids exert their activity, their effect on tumorigenesis and cancer biology remains poorly understood. The RAR receptors

Table 1
Human nuclear receptors and ligands

Receptor	Ligand(s)
Retinoic acid receptor (RAR) α, β, γ	All-*trans* retinoic acid, 9-*cis* retinoic acid, isotretinoin, etretinate, acitretin
Retinoic X receptor (RXR) α, β, γ	9-*cis* retinoic acid, bexarotene
Thyroid hormone receptor (TR)	Thyroid hormone
Vitamin D3 receptor (VDR)	Vitamin D, calcitriol
Peroxisome proliferator-activated receptor (PPAR) α, β, γ	Fatty acids, fibrates, leukotriene B4, thiazolidinediones
Pregnane X receptor	Xenobiotics
Liver X receptor α, β (LXR)	Oxysterols
Estrogen receptor α, β	Estradiol
Progesterone receptor	Progesterone
Glucocorticoid receptor	Cortisol, corticosteroids
Mineralocorticoid receptor	Aldosterone, spironolactone
Androgen receptor	Testosterone

Data from Sokołowska-Wojdyło M, Ługowska-Umer H, Maciejewska-Radomska A. Oral retinoids and rexinoids in cutaneous T-cell lymphomas. Postepy Dermatol Alergol 2013;30:19–29.

bind only to all-*trans* retinoid acid, 9-*cis* retinoic acid or synthetic isotretinoin, etretinate, and acitretin. The RXR receptors exclusively bind to 9-*cis* retinoic acid or synthetic retinoids such as bexarotene (which is often referred to as a rexinoid).[3,15] These receptors can form homodimers or heterodimers with each other or with other nuclear hormone receptors, such as thyroid hormone receptor or liver X receptor. The RXR receptor also can form a tetramer in its resting state. Once bound to a ligand, the receptor induces a conformation change forming a ligand-receptor complex. These complexes bind directly to specific DNA sequences called hormone response elements that affect transcription of specific genes and production of specific peptides downstream, which can induce and maintain terminal differentiation of malignant cells.[1,16] **Fig. 1** is a diagram demonstrating possible combinations of receptor dimers formed by rexinoid receptors.

Retinoids also have been shown to inhibit ornithine decarboxylase activity, an enzyme that is upregulated in the presence of tumor-promoting substances.[17] It is believed that retinoids also promote the production of gap junctions, which are lost during malignant transformation, as well as their glycoproteins, which aid in cell communication, adhesion, and growth.[16]

Rexinoids, such as bexarotene, bind exclusively to the RXR, and its activation has been shown to induce apoptosis involving activation of the caspase pathway. Bexarotene has been shown to activate caspase-3, a key executor of the apoptotic pathway, with resultant apoptosis as evidenced by increased poly (ADP-Ribose) polymerase and downregulation of survivin (a suppressor of caspase-induced apoptosis).[8] Retinoids reduce expression of Bcl-2 protein and upregulate bax proteins, which also are involved in apoptotic pathways.[18] Activation of RXR receptor also has been associated with activation of p53, a tumor suppressor protein, by facilitating its binding to promoters leading to cell cycle arrest.[19] Other antitumor effects of rexinoids include reduction in matrix metalloproteinases, vascular endothelial growth factor, and epidermal growth factor, which are important factors in angiogenesis as well as tumor cell migration and invasion.[20]

Various investigators have reported the immunomodulatory effects of retinoids and rexinoids. RARs are constitutively expressed in human T and B lymphocytes. Activation of RAR γ has been shown to promote CD8+ T-cell responses.[15] Retinoids upregulate Langerhans cell antigen presentation and surface expression of HLA-DR and CD11c, which is important for T-cell activation.[21] Retinoids and rexinoids also have been shown to upregulate interleukin-2 receptor (IL-2R) expression with associated increase in interferon (IFN) γ levels.[22] Gorgun and Foss[4] reported elevation in IL-2R levels in human T-cell and B-cell leukemia cell lines after treatment with rexinoids. In the same study, they reported the upregulation of IL-2R in the malignant cells translated to increase sensitivity to denileukin diftitox (a fusion protein of diphtheria toxin bound to the ligand for the IL-2R previously used in the treatment of CTCL).[4,23]

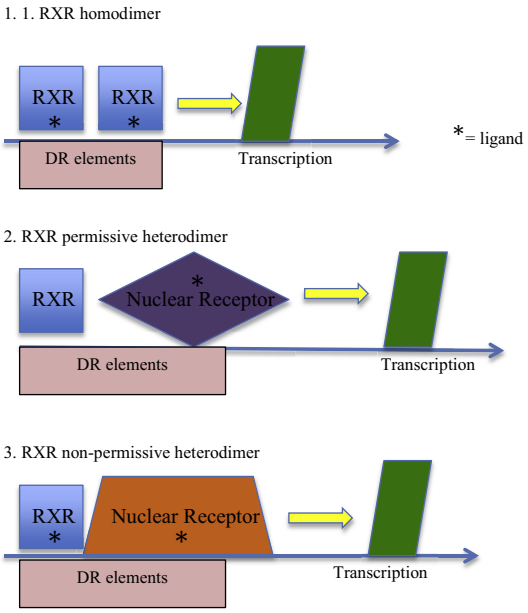

Fig. 1. Retinoid receptor responses. (1) RXR forms homodimers with itself, and with ligand binding, leads to activation of transcription. (2) RXR also forms permissive heterodimers with other nuclear receptors, such as PPAR and LXR-activation of transcription occurs with binding of ligand to either receptor. (3) RXR forms nonpermissive heterodimers with RAR, TR, or VDR. Activation of transcription occurs only with ligand binding on both receptors. DR elements, direct repeat elements; TR, Thyroid hormone receptor; VDR, vitamin D3 receptor. [a] Ligand.

RETINOIDS IN CUTANEOUS T-CELL LYMPHOMA

Currently all systemic retinoids in use for CTCL are oral agents (administered with food for optimal absorption). Isotretinoin was the first retinoid used for the off-label treatment of CTCL. In 1983, Kessler and colleagues[11] first reported activity in 4 patients with MF treated with isotretinoin at doses of 1 to 3 mg/kg per day with response seen in all patients, 1 patient with a complete response (CR). The investigator proceeded to study 21 additional patients with plaque, tumor, and erythrodermic MF,

including 5 with SS using doses of 1 to 2 mg/kg per day.[24] Forty-four percent of patients were reported to have a clinical response, but most patients required dosage adjustment because of mucocutaneous side effects.[24] In 2005, Leverkus and colleagues[25] reported effective treatment of folliculotropic MF with isotretinoin at up to 1 mg/kg per day with specific regard to miniaturization of cysts and comedones associated with this subtype. This effect may be due to the strong affinity of isotretinoin for the pilosebaceous unit. Higher doses of isotretinoin (eg, >1 mg/kg per day) produced similar response rates with higher rates of toxicity compared with 1 mg/kg per day.[24] Overall, use of isotretinoin in MF/SS resulted in clinical responses of 43% to 100% with CR rates of typically less than 20% and short response duration ranging from 3 to 15 months.[3]

Etretinate was the second retinoid approved for clinical applications, originally approved for use in psoriasis. It is highly lipophilic and has a significantly longer half-life of more than 120 days compared with 21 hours with isotretinoin and requires 2 or more years to be completely eliminated from the body after completion of treatment. As such, it was replaced by its metabolite acitretin with a shorter half-life of 2 to 4 days and an elimination period of approximately 2 months (though alcohol ingestion can cause acitretin to convert to etretinate and should be avoided during acitretin use).[26] Before the withdrawal of etretinate from the market in 1998, several studies reported responses in patients with MF when used off-label. Claudy and colleagues[27] treated 12 patients with etretinate monotherapy using 0.8 to 1.0 mg/kg per day with response seen in all patients, but only 1 patient achieved a CR. Clinical response was seen in 55% of patients treated with etretinate in a larger study of 29 patients reported by Molin and colleagues[28] with CR seen in only 1 patient. The treatment response with etretinate appears to be similar to that reported with isotretinoin.

Cheeley and colleagues[29] reported a retrospective study on the use of acitretin in 32 patients with MF/SS. There was a 59% overall response rate with 1 patient achieving CR, but the interpretation of these results may be confounded by other concomitant treatments received by the patients. Acitretin was used as monotherapy in only 6 patients with MF in the study, with clinical response seen in approximately 25% of these patients. The investigators in the retrospective review attempted to compare response between acitretin and bexarotene in patients treated with both medications at different times in their treatment course, but timing of use in the disease course and other concomitant treatment may influence therapeutic outcome, making comparison difficult. There is limited experience with acitretin in MF (doses used typically 10–50 mg daily), but anecdotal evidence suggests that it may be less effective in these patients than the other RAR agonists or bexarotene, but few comparative studies exist.[1] All-*trans* retinoic-acid has been shown in vitro to have beneficial effects in CTCL and has also been used off-label for CTCL.[30,31]

Bexarotene is a synthetic rexinoid with RXR selective binding. Unlike its predecessor retinoids, it was approved by the Food and Drug Administration (FDA) specifically for the treatment of CTCL in 1999. Bexarotene was investigated in 2 phase II-III trials in 58 patients with early-stage (I-IIA) MF and in 94 patients with advanced-stage (IIB-IVB) MF/SS.[32,33] In the early-stage trial, patients were treated at dosages ranging from 6.5, 300, and 650 mg/m^2 per day, but the 300 mg/m^2 per day dosage was found to be the ideal starting dose due to toxicity.[3] Clinical responses in this study were reportedly 20%, 54%, and 67% in the 6.5, 300, and 650 mg/m^2 per day treatment groups, respectively.[32] Of the advanced-stage patients, 56 were treated at a dosage of 300 mg/m^2 per day and 38 at a dosage of more than 300 mg/m^2 per day. Patients treated at 300 mg/m^2 per day had clinical responses in 45% (25 of 56) of patients compared with 55% (21 of 38) of patients in the higher-dose treatment group, suggesting that there is a dose-related treatment response. The CR rates for the 300 mg/m^2 per day group was 2% compared with 13% in the higher-dose group. The median time to response was 180 days and time to progression was projected to be 299 days for the lower-dose group and 385 days for the higher-dose group. Among patients with a history of previous retinoid therapy who had not previously responded to other retinoids or had previously responded but progressed, a large portion (54%) improved with bexarotene. More adverse reactions were reported in the higher-dose group with approximately13% of patients in this group discontinuing treatment because of side effects compared with 7% in the lower-dose group.[33] Another large retrospective trial was reported by Abbott and colleagues[34] in 66 patients with MF and SS with most patients having advanced-stage MF/SS (IIB-IVB). Patients were included if they had received 150 to 300 mg/m^2 daily within the study period. Other treatment modalities, such as radiation or extracorporeal photopheresis (ECP), were used in some patients. Twenty-eight patients completed at least 1 month of treatment with bexarotene as monotherapy, and in these patients, 46% achieved a clinical response, with 14% (4 patients) achieving a CR and 32% (9 patients)

achieving a partial response (PR). In patients treated with bexarotene in combination with other treatment modalities, the CR rate was 5% and PR rate was 37%. Bexarotene appears to have more potent activity in MF compared with its predecessors, but not all patients respond to monotherapy and some fail to maintain remission, prompting investigation into its use in combination with other agents. Bexarotene is available as a 75-mg capsule.

Alitretinoin is another synthetically derived retinoid (9-*cis* retinoic acid), which can bind to both RAR and RXR, hence its classification as a pan-retinoic receptor agonist.[1] It was approved in 1999 by the FDA for topical use in localized AIDS-related Kaposi sarcoma and has been available in Europe since 2008 as an oral formulation for the treatment of refractory severe chronic hand dermatitis.[35,36] Oral alitretinoin has been used for treatment of MF as reported in a case series of 2 patients, 1 with refractory disease, resulting in PRs and no significant side effects.[37] More recently, a retrospective study described efficacy of alitretinoin (10 or 30 mg daily) when combined with other therapies (including topical steroids, topical calcineurin inhibitors, phototherapy, IFN-alpha, and/or photopheresis) in 10 patients with MF (stages IA–IIB) and 1 patient with SS (4 CRs and 6 PRs). Side effects were uncommon and included headache, dyslipidemia, and low thyroid-stimulating hormone (TSH) without other thyroid abnormalities.[38] This drug holds significant promise for the treatment of MF/SS, but further studies are needed to investigate its efficacy and safety in this patient population.

Retinoids also have been studied in combination with other treatment modalities (both skin directed and other systemic agents) in MF/SS in an attempt to improve response rates, prolong remission, and decrease adverse effects by using lower doses with nonoverlapping toxicities. Of note, the limitation of these combination studies are that most of them were not controlled, were without comparator arm, had a limited number of patients, and were performed before International Society of Cutaneous Lymphomas (ISCL)/European Organization for the Research and Treatment of Cancer (EORTC) revisions in CTCL staging (2007) and ISCL/EORTC/US Cutaneous Lymphoma Consortium uniform response criteria definitions (2010), thus making it difficult to accurately compare response rates.[39,40] Furthermore, because of the paucity of data, it remains unclear if combination therapies are definitively superior to monotherapy.[41]

Systemic retinoids combined with skin-directed therapy, such as phototherapy (ultraviolet B [UVB]) or psoralen with ultraviolet A phototherapy (PUVA), referred to as Re-UVB or Re-PUVA are well-known combination therapies for many skin conditions (psoriasis, eczema). In MF/SS, isotretinoin was studied in combination with PUVA, with high response rates in 66 patients, with CR in 72% of patients. Although the clinical response was similar to PUVA alone, the study found that fewer UVA treatments were needed for response when the combination was used.[42] PUVA also was combined with acitretin in 42 patients with CTCL, producing a CR rate of 38%. This was significantly lower compared with the comparator arm of PUVA with IFN, which had a CR rate at 70%.[43]

Despite occasional association with photosensitivity in the early clinical studies, since its FDA approval in 1999, bexarotene has been combined successfully with phototherapy in patients with CTCL. In patients with MF stage IA-IIB, combination of low-dose bexarotene (75 mg per day) with PUVA led to clinical response in all patients with CR seen in 63% of patients.[44] In a prospective study of 14 patients with relapsed or treatment-refractory MF (stage IA-III), patients were treated with bexarotene at 150 to 300 mg per day concurrently with PUVA. Overall response rate was 67%, with 29% CRs.[45] In a large randomized controlled trial comparing PUVA versus bexarotene plus PUVA (EORTC 21011), 87 patients with stage IB/IIA MF were randomized to each treatment group but no significant difference in response rate (71% PUVA vs 77% combination arm) or response duration (9.7 PUVA vs 5.8 months combination) was found.[46]

Bexarotene also has been combined with narrow-band UVB (NBUVB) therapy in case reports. One patient with stage IB plaque-stage MF was treated successfully with low-dose bexarotene (75 mg daily) and NBUVB treatment 3 times weekly. The patient was previously treatment refractory and NBUVB was used in place of PUVA because of the history of multiple basal cell carcinomas.[47] Another case report in a patient with plaque-stage MF responded to a combination of bexarotene 300 mg daily with NBUVB. The disease flared when either bexarotene or NBUVB was discontinued, suggesting a possible synergistic or additive effect.[48]

Combination trials using retinoids with other systemics, such as IFNs, have been reported by various investigators. This combination is attractive because of synergistic effects of retinoid stimulation of Th1 activity through IL-12 production and inhibition of Th2 response by IFN-alpha and IFN-gamma.[49] Isotretinoin at 1 mg/kg per day was combined successfully with IFN-alfa-2b 2 million units (MU) 3 times weekly in 7 patients

with clinical objective response (OR) seen in 57% of patients (29% achieving CR).[50] Isotretinoin also was studied in combination with IFN-alfa as induction therapy together with total-body electron beam radiation and chemotherapy in 28 patients. Overall response in this study was 82%, with 71% achieving CR.[51] Isotretinoin at 1 mg/kg per day has been investigated in combination with 3 MU daily of IFN-alfa in 18 patients with MF/SS.[52] Patients in this study had advanced-stage disease (IIB-IV) and were found to have OR rates of 33% with half the responders having SS. It appears that the combination was well tolerated.

Bexarotene has been investigated in a phase II trial in combination with IFN-alfa in 22 patients with MF/SS. Most of the patients in this study had advanced-stage disease (with 86% of patients having stage II-IV disease). Patients were treated initially with bexarotene 300 mg/m^2 per day alone for 8 weeks followed by the addition of IFN-alfa-2b at 3 to 5 MU 3 times weekly for 8 additional weeks if CR was not achieved with bexarotene alone. No patient achieved CR during the first 8 weeks of treatment with bexarotene alone. The overall response rate was 39%, with 1 patient achieving CR. Of note, 4 additional responses were observed with the addition IFN in the second stage of the study, with 1 patient initially having PR to bexarotene alone converting to CR.[53]

ECP is a treatment modality highly effective in patients with SS with treatment responses as a monotherapy reported at 60% and 19% CR.[54] Bexarotene at dosages ranging from 225 to 750 mg per day or up to 300 mg/m^2 daily in combination with ECP led to high response rates of 75% to 80% in small studies.[49,55] In another study in patients with SS, bexarotene at 150 mg per day was added, as part of a multimodality approach to treatment, to monthly ECP, PUVA with and without IFN-gamma or alfa 3 times weekly producing CRs in 3 of 5 patients and PR in the other 2 patients.[56]

Retinoids and rexinoids also have been used in combination with other biologic and chemotherapeutic agents active against MF/SS. The combination of bexarotene in combination with denileukin diftitox is believed to be synergistic, as retinoids have the ability to enhance the expression of high-affinity IL-2 receptor and thereby increase the susceptibility to denileukin diftitox.[4] This effect was observed at bexarotene dosages of 150 mg per day or higher. Fourteen patients with MF/SS treated with the combination of bexarotene 75 to 375 mg per day and denileukin diftitox 18 μg/kg per day 3 times every 21 days, had an overall response rate of 67%, including 29% with a CR.[57] Bexarotene was studied in combination with vorinostat, a histone deacetylase inhibitor, in a combination phase I/II study in 23 patients with MF/SS in stages IB or higher. The maximum tolerated dosage in the phase I part of the study was 200 mg per day of vorinostat and 300 mg/m^2 per day of bexarotene. Patients in the phase II part of the study were treated with 400 mg per day of vorinostat and 150 mg/m^2 per day of bexarotene. Overall response was 26% (7% in phase I of the study and 33% in phase II). This OR rate was similar to patients treated with vorinostat monotherapy. However, improvement in pruritus was reported in several patients. More than 20% of patients required discontinuation from the trial because of adverse effects, but adverse effects reported (neutropenia, diarrhea, hypertriglyceridemia) did not appear to correlate with the higher dosages used in the second phase of the study.[58]

Bexarotene also has been studied in MF/SS in combination with chemotherapy agents, such as methotrexate (MTX) and pralatrexate. In a retrospective study of 12 patients with MF (stage IA-IIB) who were treated with bexarotene at dosages of 75 to 300 mg per day and MTX at 5 to 30 mg per week, overall response was 66% with 8% achieving CR.[59] Another study compared pralatrexate with the combination of bexarotene at 150 to 300 mg/m^2 daily and pralatrexate 15 mg/m^2 weekly. Overall response was seen in 33% of patients treated with pralatrexate alone compared with 50% in the combination group.[60] Clinical responses with the combination appear to be higher compared with the individual chemotherapy agents alone. However, not all combination trials demonstrate increased efficacy with the addition of retinoids. In a recently published study evaluating the combination of gemcitabine at 1000 mg/m^2 intravenously on days 1 and 8 every 21 days with oral bexarotene at 300 mg/m^2 per day in 35 predominantly advanced-stage (IB-IVA) CTCL, resulted in interruption of the trial when lower responses were revealed at interim analysis when compared with single-agent gemcitabine.[61] The prominent studies involving the retinoids and rexinoid for treatment of MF/SS are listed in **Table 2**.

Resistance to retinoids has been reported in the literature. In vitro evaluation of malignant T cells found that malignant cells from as high as 33% of patients with SS are intrinsically resistant to bexarotene.[62] The mechanism of bexarotene resistance was investigated in a patient who initially responded to treatment but later developed disease relapse. Malignant T cells obtained from this patient at baseline underwent apoptosis with exposure to bexarotene, but cells obtained at relapse did not. No genetic coding alterations in the RXR receptors were found to suggest that mutation of the receptor was responsible for loss

Table 2
Notable studies of retinoids and rexinoids in CTCL

Treatment	No. of Patients	Stage of CTCL	Dose	Response Rate	Author, Year
Isotretinoin	25	MF 20/SS 5	1–2 mg/kg/d	OR 44%; CR12%	Kessler et al,[24] 1987
Isotretinoin	7	NA	100 mg/m^2 daily	OR 43%; CR 14%	Warrell et al,[12] 1983
Isotretinoin	15	MF 10/SS 5	0.2–2 mg/kg/d	OR 59%; CR 21%	Molin et al,[28] 1987
Isotretinoin	20	MF 16/SS 4	1–2 mg/kg/d	OR 80%; CR 33%	Thomsen et al,[72] 1984
Isotretinoin	6	MF 6/SS 1	1–2 mg/kg/d	OR 100%; CR none	Neely et al,[73] 1987
Isotretinoin + interferon-alpha	7	MF 7	1 mg/kg/d (isotretinoin) + 2 million units/d (interferon-alpha-2b)	OR 57%; CR 29%	Knobler et al,[50] 1991
Isotretinoin + interferon-alpha	18	MF 12/SS 6	1 mg/kg/d (Isotretinoin) + 3 million units/d (interferon-alpha-2b)	OR 33%; CR 6%	Tsimberidou et al,[52] 2004

(*continued on next page*)

Table 2
(*continued*)

Treatment	No. of Patients	Stage of CTCL	Dose	Response Rate	Author, Year
Isotretinoin + interferon-alpha + TSEB/CT	28	MF 23/SS 5	1 mg/kg/d (isotretinoin) + 5 million units/d (interferon-alpha-2b) followed by TSEB/CT	OR 82%; CR 71%	Duvic et al,[51] 1996
Isotretinoin + PUVA	69	MF 69	1 mg/kg/d isotretinoin + PUVA	CR 73%	Thomsen et al,[42] 1989
Etretinate	12	Parapsoriasis, MF, SS	0.8–1 mg/kg/d	OR 100%; CR 8%	Claudy et al,[27] 1983
Etretinate	29	MF/SS	NA	OR 55%; CR 21%	Molin et al,[28] 1987
Acitretin	32 (only 6 as monotherapy)	MF 29/SS 2/ Unspecified 1	10–50 mg daily	OR 25%; CR none (monotherapy)	Cheeley et al,[29] 2013
Bexarotene	94	MF 77/SS 17 Advanced stage	300 mg/m^2/d and more than 300 mg/m^2/d	OR 45%; CR 2% (300 mg/m^2/d) vs OR 55%; CR 13% (>300 mg/m^2/d)	Duvic et al,[33] 2001
Bexarotene	58	MF 58 (early stage)	6.5, 300, 650 mg/m^2/d	OR 20%; CR none, OR 54%; CR 7%, and OR 67%; CR 27% in the 6.5, 300, and 650 mg/m^2/d respectively	Duvic et al,[32] 2001
Bexarotene	66 (only 28 as monotherapy)	MF 25/SS 3	150–300 mg/m^2/d	OR 46%; CR 14%	Abbott et al,[34] 2009
Bexarotene + interferon-alpha	22	CTCL (IB-IV)	300 mg/m^2/d (Bexarotene) + interferon-alpha-2b 3 million units 3 times weekly	OR 39%; CR 6%	Straus et al,[53] 2007
Bexarotene + NBUVB	1	MF 1 (IB)	75 mg/d (Bexarotene) + NBUVB	Improvement	D'Acunto et al,[47] 2010
Bexarotene + NBUVB	1	MF 1 (1B)	150, increased to 300 mg/d + NBUVB	Improvement	Lokitz & Wong,[48] 2007
Bexarotene + PUVA	14	MF 12/SS 2	150–300 mg/d (Bexarotene) + PUVA	OR 67%; CR 29%	Papadavid et al,[45] 2008

Bexarotene + PUVA	8	MF 8 (IA-IB)	75 mg/d (Bexarotene) + PUVA	OR 100%; CR 63%	Singh & Lebwohl et al,[44] 2004
Bexarotene + PUVA vs PUVA	87	MF 87 (IB-IIA)	Dosage not reported (Bexarotene) + PUVA	OR 71%; CR 22.2% (PUVA) vs OR 77%; CR 31.3% (Combination)	Whittaker et al,[46] 2012
Bexarotene + vorinostat	23	CTCL (stage IB or higher)	150–300 mg/m^2/d (Bexarotene) + 200–400 mg/d vorinostat	OR 26%;(CR not reported)	Dummer et al,[58] 2012
Bexarotene + ECP	5	MF 3/SS 2	300 mg/m^2/d (Bexarotene) + PUVA	OR 80%; CR 20%	Tsirigotis et al,[55] 2007
Bexarotene + ECP	8	MF/SS	100–300 mg/m^2/d (Bexarotene) + ECP	OR 75%; CR 13%	Talpur et al,[49] 2002
Bexarotene + denileukin diftitox	14	CTCL (IA-IVB)	75–375 mg/d (Bexarotene) + 18 μg/kg/d × 3 d q21 d	OR 67%; CR 29%	Foss et al,[57] 2005
Bexarotene + methotrexate	12	MF (Stage IA-IIB)	75–300 mg/d (Bexarotene) + methotrexate 5–30 mg/wk	OR 66%; CR 8%	Kannangara et al,[59] 2009
Bexarotene + gemcitabine	35	CTCL (IB-IVB)	300 mg/m^2/d (bexarotene) + 1000 mg/m^2 D1&8 q21 d (gemcitabine)	OR 31%; CR none Lower than single agent gemcitabine	Illidge et al,[61] 2013
Bexarotene + pralatrexate	14	MF	150–300 mg/m^2/d (bexarotene) + 15 mg/m^2/wk (pralatrexate)	OR 50%; CR none	Talpur et al,[60] 2014
Alitretinoin	2	MF 2	30 mg/d	OR/PR 100%	Coors & von den Driesch,[37] 2012
Alitretinoin	11	MF 10 (IA-IIB)/SS 1	10 or 30 mg daily	OR 91%; CR 40%	Kapser et al,[38] 2015

Abbreviations: CR, complete response; CT, chemotherapy; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; NA, not available; NBUVB, narrow band UVB; OR, objective response; PR, partial response; PUVA, psoralen plus UVA; SS, Sézary syndrome; TSEB, total-body skin electron beam radiation.

of activity. A decline in the levels of RXR receptor expression on cells, which is the receptor target for bexarotene, was found as a possible mechanism.[63]

ADVERSE EFFECTS

Retinoids have a unique side-effect profile compared with traditional cytotoxic agents. In clinical studies of bexarotene, the most common adverse effects are dyslipidemia, which has been reported to occur in 100% of patients, and secondary hypothyroidism, reported in 40% to 100% of patients taking bexarotene.[1] Other common side effects of bexarotene include liver function test abnormalities and dose-dependent leukopenia and neutropenia, and rarely, gastrointestinal disturbances. Dyslipidemia also is common in patients receiving isotretinoin. **Table 3** is a list of common side effects associated with bexarotene. In contrast to the adverse effects seen in RXR agonists, side effects associated with RAR agonists seen in clinical studies in patients with CTCL include xerosis (dose-limiting), cheilitis, headaches, and arthralgias/myalgias. See **Table 4** for side effects associated with isotretinoin. Because of teratogenic effects, all retinoids and rexinoids should be avoided in pregnant patients or in patients who wish to become pregnant.

Dyslipidemia is a dose-dependent and sometimes dose-limiting adverse reaction to both retinoids and rexinoids. This is typically manifested as hypertriglyceridemia and less commonly hypercholesterolemia. Activation of RAR leads to secretion and decreased catabolism of triglyceride particles leading to hypertriglyceridemia and resulting decrease in high-density lipopoprotein.[64] The binding of agonists to RXR has been shown to result in increased apoCIII synthesis, a hepatic protein that binds to lipids in the plasma and aids in hepatic uptake of triglyceride particles. It also decreases lipoprotein lipase activity, which hydrolyzes triglycerides into fatty acids.[65] Peroxisome proliferator–activated receptors (PPARs) are nuclear hormone receptors that are part of the superfamily of receptors that also includes retinoid receptors and others. These receptors are strongly expressed in the skin and sebaceous glands and are involved in oxidative pathways for fatty acids.[65] Retinoic X receptors form heterodimers with PPARs and transactivation by rexinoids are believed to influence lipid metabolism.[1] Triglyceride elevation also is regulated by transactivation of LXR (Liver X receptor)/RXR heterodimers by sterol regulatory element–binding proteins, which are transcription regulators involved in cholesterol biosynthesis.[1] The LXR acts by controlling cholesterol metabolism in the liver as well as reverse cholesterol transport from the peripheral tissues to the liver by increasing plasma lipids. Activation of LXR on RXR heterodimers may play only a small part in the complex pathway of the influence retinoids have on metabolism of not only lipids, but also of glucose and fatty acids.[1] In patients

Table 4
Moderate to severe side effects of isotretinoin

Side Effects	Prevalence/Moderate/Severe, %
Xerosis	36/20
Chelitis	28/0
Conjunctivitis	36/0
Fatigue	12/8
Arthralgia/Myalgia	8/8
Mental status change	8/0
Headache	8/0

Data from Kessler JF, Jones SE, Levine N, et al. Isotretinoin and cutaneous helper t-cell lymphoma (mycosis fungoides). Arch Dermatol 1987;123:201–4.

Table 3
Side effects of bexarotene

Side Effect	Prevalence, %
Central hypothyroidism	29–100
Hypertriglyceridemia	82–100
Dyslipidemia (increased low-density lipoprotein; decreased high-density lipoprotein)	30
Liver toxicity	11–20
Headache	16–20
Skin rash, phototoxicity	8–13
Leucopenia	6–11

Adapted from Graeppi-Dulac J, Vlaeminck-Guillem V, Perier-Muzet M, et al. Endocrine side-effects of anti-cancer drugs: the impact of retinoids on the thyroid axis. Eur J Endocrinol 2014;170:R256.

receiving bexarotene as monotherapy at 300 mg/m^2 daily, hypertriglyceridemia was found in 83% of patients, with 2 of 70 patients developing pancreatitis due to the markedly elevated triglyceride levels.[49] Of interest, it was reported by Talpur and colleagues[49] in 2002 that higher response rates to bexarotene were associated with use of lipid-lowering agents, with the highest response rates seen in patients treated with atorvastatin and fenofibrate. The higher response rate in these patients may be merely a reflection of the higher doses of bexarotene used (as dyslipidemia is a dose-dependent phenomenon) or perhaps higher sensitivity to bexarotene, which parallels dose response. In contrast, patients who were treated with the lipid-lowering agent gemfibrozil had more severe hypertriglyceridemia and elevated bexarotene serum levels. Its use is contraindicated with bexarotene because it inhibits the oxidative metabolism of the drug, thereby increasing toxicity.[49] In one case series of 102 subjects on isotretinoin, patients with predisposing conditions, such as truncal obesity, hyperinsulinemia, or family history of hypertriglyceridemia, were more likely to develop retinoid-induced hypertriglyceridemia.[66] Patients receiving either isotretinoin or bexarotene should have baseline lipid evaluation before starting therapy and close monitoring should take place during treatment. In most patients treated with bexarotene, treatment with lipid-lowering agents and adherence to low-fat and low-cholesterol diet are recommended at the onset of treatment.

Central hypothyroidism also is commonly encountered in patients treated with bexarotene. This is caused by suppression of the pituitary production of the TSH. RXRγ is the subtype of receptor implicated in rexinoid-induced hypothyroidism and is strongly expressed in the pituitary. In contrast, isotretinoin and acitretin, RAR agonists, do not have effects on TSH levels and hypothyroidism.[2] Alitretinoin affects both RAR and RXR receptors, so it also may have effects on the thyroid hormone axis. Similar to retinoid-induced hyperlipidemia, bexarotene-induced hypothyroidism also appears to be dose dependent and reversible. In patients with normal thyroid function before starting treatment with bexarotene, serum TSH returns to normal in most patients as early as 8 days after stopping bexarotene.[67] Because bexarotene patients typically require doses higher than replacement thyroid doses used in hypothyroidism from other causes, it has been suggested that an increase in metabolism of thyroid hormone also may play a role, perhaps through induction of liver metabolic oxidative enzymes by retinoids.[2,68] Patients should be started on empiric thyroid supplementation at onset of treatment with bexarotene (25–50 μg daily) and increased based on monthly serum-free thyroxine (free T4) levels. TSH remains suppressed while on bexarotene, even with adequate levothyroxine supplementation so the TSH should not be used as the basis by which one adjusts levothyroxine dose.

Dose-dependent leukopenia and neutropenia can be observed in 10% of patients, but in contrast to neutropenia observed after cytotoxic chemotherapy, bexarotene neutropenia is not typically associated with increased opportunistic infections because neutrophils are functionally normal. Given this, in our patients with MF/SS who have no previous history of cytotoxic chemotherapy, we do not dose reduce bexarotene unless absolute neutrophil count is less than 500/μL (Ellen Kim, personal communication, 2015).

Alitretinoin has been associated with a lower incidence of dyslipidemia and/or suppression of the thyroid axis as compared with isotretinoin or bexarotene, usually not requiring treatment for these side effects.[35] The mechanism explaining this difference in side-effect profile is not known.[37]

No definitive guidelines exist for monitoring or management of adverse effects associated with retinoids and rexinoids. Isotretinoin is contraindicated in patients who are pregnant and should be used with caution in patients who have history of uncontrolled psychiatric illness, inflammatory bowel disease, and osteoporosis. Patients who are being treated with isotretinoin in the United States should follow monitoring as per the iPLEDGE (a mandatory distribution program for isotretinoin in the United States) program. This includes pregnancy monitoring for female patients with childbearing potential at baseline and monthly. Patients receiving isotretinoin should avoid concomitant use of tetracycline class of antibiotics due to the increased risk of pseudotumor cerebri. We also recommend baseline laboratory testing such as complete blood count, liver function tests, and lipid profile while on therapy. Acitretin and bexarotene are also contraindicated in pregnancy and should be used with caution in patients with liver disease, history of alcohol abuse, or uncontrolled hyperlipidemia. Female patients should avoid becoming pregnant for at least 3 years after discontinuation of the acitretin. This should be considered before initiation of treatment in any female patient who is of childbearing age. Use of alcohol during treatment with acitretin results in conversion of acitretin to etretinate and can result in prolonged elimination of the retinoid.[69]

In patients on treatment with bexarotene, additional monitoring of free thyroxine (free-T4) levels and not TSH is required (TSH is typically suppressed in central hypothyroidism and is not

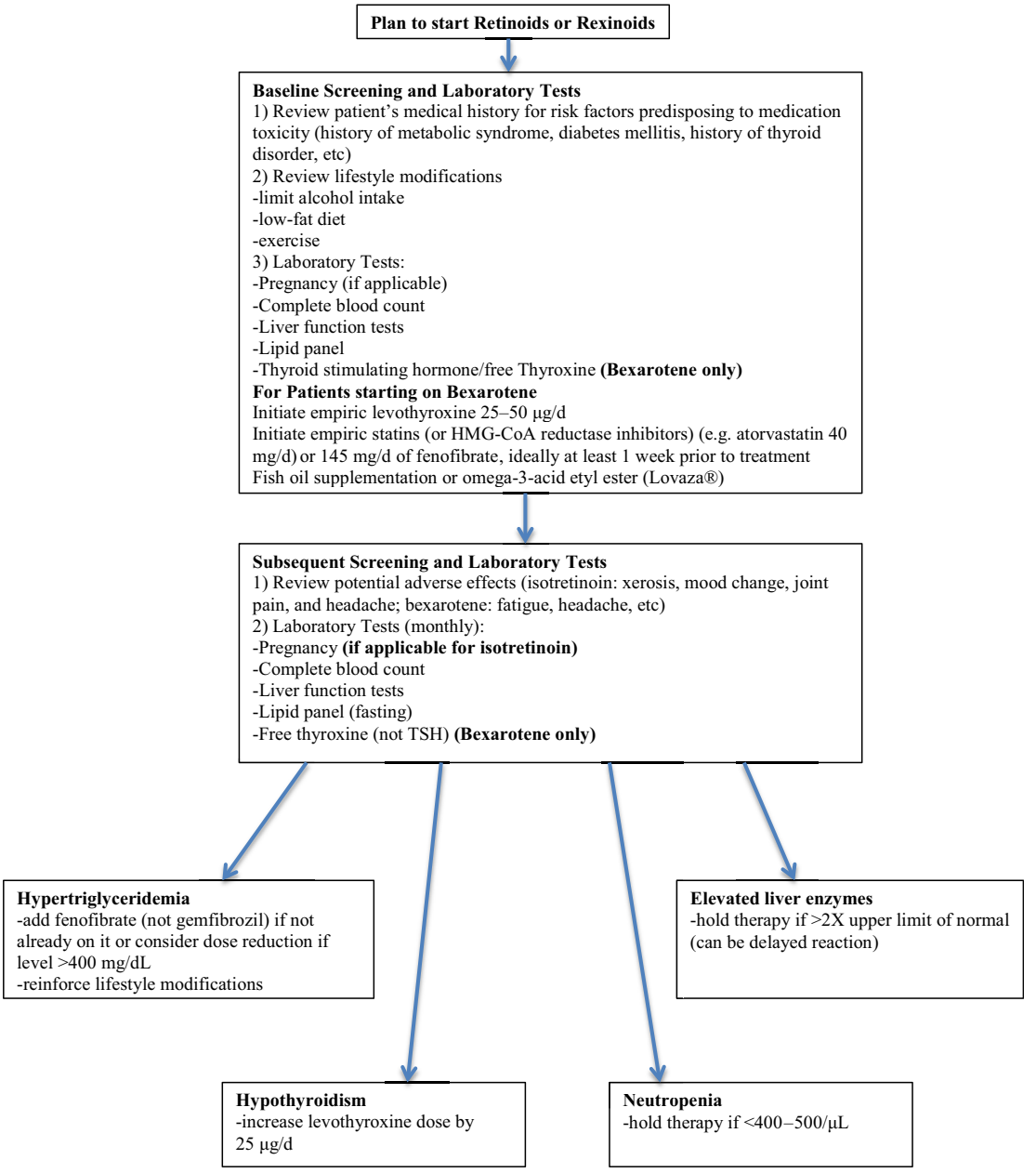

Fig. 2. Recommendations for monitoring patients on systemic retinoids.

reliable as a measure of thyroid function in patients on the medication). Bexarotene should not be given in combination with gemfibrozil because of increases in plasma concentration of bexarotene. It is metabolized in the liver via cytochrome p-450 3A4 and when used in combination with 3A4 inhibitors, such as azole class of antifungal agents (ketoconazole, itraconazole) or grapefruit juice or with 3A4 inducers, such as rifampin or phenytoin, alterations in plasma levels of the drug may occur.[70] In all patients receiving retinoids, lifestyle modifications, including exercise and dietary changes that include low-fat diet and limits on alcohol consumption should be advised. Recommended monitoring and management of adverse effects for patients on retinoids and rexinoids are shown in **Fig. 2**.[71]

SUMMARY

MF and SS subtypes of CTCL have a variable clinical course ranging from indolent disease that

does not alter life expectancy to aggressive, rapidly progressive disease. Goals of treatment especially in patients with early-stage disease are to induce remission with agents that have a low toxicity profile. The systemic retinoids are an important component of the treatment options for all stages of this disease because of the ease of administration and relative low toxicity profile. Side effects appear to be dose related and should be monitored closely with hyperlipidemia observed with all retinoids, whereas other side effects are more drug or retinoid class specific. For example, central hypothyroidism appears to be limited to RXR agonists and mucocutaneous dryness to RAR agonists. Bexarotene is the only FDA-approved systemic retinoid approved specifically for CTCL but does require additional medications to treat the associated hyperlipidemia and hypothyroidism during the duration of bexarotene treatment. Combination treatment with retinoids and other agents with activity against MF/SS appear to be well tolerated and associated with high response rates in relapsed or treatment-refractory patients in small studies and series. Further high-quality clinical trials are needed in MF/SS patients to confirm whether combination therapies are superior to monotherapy.

REFERENCES

1. Sokołowska-Wojdyło M, Ługowska-Umer H, Maciejewska-Radomska A. Oral retinoids and rexinoids in cutaneous T-cell lymphomas. Postepy Dermatol Alergol 2013;30:19–29.
2. Graeppi-Dulac J, Vlaeminck-Guillem V, Perier-Muzet M, et al. Endocrine side-effects of anti-cancer drugs: the impact of retinoids on the thyroid axis. Eur J Endocrinol 2014;170:R253–62.
3. Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264–71.
4. Gorgun G, Foss F. Immunomodulatory effects of RXR rexinoids: modulation of high-affinity IL-2R expression enhances susceptibility to denileukin diftitox. Blood 2002;100:1399–403.
5. Kempf W, Kettelhack N, Duvic M, et al. Topical and systemic retinoid therapy for cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 2003;17:1405–19.
6. Tang X-H, Gudas LJ. Retinoids, retinoic acid receptors, and cancer. Annu Rev Pathol 2011;6:345–64.
7. Cheng AL, Su IJ, Chen CC, et al. Use of retinoic acids in the treatment of peripheral T-cell lymphoma: a pilot study. J Clin Oncol 1994;12:1185–92.
8. Zhang C, Hazarika P, Ni X, et al. Induction of apoptosis by bexarotene in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. Clin Cancer Res 2002;8:1234–40.
9. Bradford PT, Devesa SS, Anderson WF, et al. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064–73.
10. National Comprehensive Cancer Network Guidelines. Non-Hodkin's Lymphoma. Version 5.2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf. Accessed February, 2015.
11. Kessler JF, Meyskens FL, Levine N, et al. Treatment of cutaneous T-cell lymphoma (mycosis fungoides) with 13-cis-retinoic acid. Lancet 1983;1:1345–7.
12. Warrell RP Jr, Coonley CJ, Kempin SJ, et al. Isotretinoin in cutaneous t-cell lymphoma. Lancet 1983;322:629.
13. Stadler R, Kremer A. Therapeutic advances in cutaneous T-Cell lymphoma (CTCL): from retinoids to rexinoids. Semin Oncol 2006;33(Supplement 3):7–10.
14. Layton A. The use of isotretinoin in acne. Dermatoendocrinol 2009;1:162–9.
15. Gordy C, Dzhagalov I, He Y-W. Regulation of CD8(+) T cell functions by RARgamma. Semin Immunol 2009;21:2–7.
16. Heller EH, Shiffman NJ. Synthetic retinoids in dermatology. Can Med Assoc J 1985;132:1129–36.
17. Boutwell RK. Retinoids and inhibition of ornithine decarboxylase activity. J Am Acad Dermatol 1982;6:796–800.
18. Burg G, Dummer R. Historical perspective on the use of retinoids in cutaneous T-cell lymphoma (CTCL). Clin Lymphoma 2000;1(Supplement 1):S41–4.
19. Nieto-Rementería N, Pérez-Yarza G, Boyano MD, et al. Bexarotene activates the p53/p73 pathway in human cutaneous T-cell lymphoma. Br J Dermatol 2009;160:519–26.
20. Yen W-C, Prudente RY, Corpuz MR, et al. A selective retinoid X receptor agonist bexarotene (LGD1069, targretin) inhibits angiogenesis and metastasis in solid tumours. Br J Cancer 2006;94:654–60.
21. Meunier L, Bohjanen K, Voorhees JJ, et al. Retinoic acid upregulates human Langerhans cell antigen presentation and surface expression of HLA-DR and CD11c, a beta 2 integrin critically involved in T-cell activation. J Invest Dermatol 1994;103:775–9.
22. Rook AH, Kubin M, Fox FE, et al. The potential therapeutic role of interleukin-12 in cutaneous T-cell lymphoma. Ann N Y Acad Sci 1996;795:310–8.
23. Sidell N, Chang B, Bhatti L. Upregulation by retinoic acid of interleukin-2-receptor mRNA in human T lymphocytes. Cell Immunol 1993;146:28–37.
24. Kessler JF, Jones SE, Levine N, et al. Isotretinoin and cutaneous helper T-cell lymphoma (mycosis fungoides). Arch Dermatol 1987;123:201–4.
25. Leverkus M, Rose C, Bröcker EB, et al. Follicular cutaneous T-cell lymphoma: beneficial effect of isotretinoin for persisting cysts and comedones. Br J Dermatol 2005;152:193–4.

26. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. J Am Acad Dermatol 1999;41:S7–12.
27. Claudy AL, Rouchouse B, Boucheron S, et al. Treatment of cutaneous lymphoma with etretinate. Br J Dermatol 1983;109:49–56.
28. Molin L, Thomsen K, Volden G, et al. Oral retinoids in mycosis fungoides and Sézary syndrome: a comparison of isotretinoin and etretinate. A study from the Scandinavian Mycosis Fungoides Group. Acta Derm Venereol 1987;67:232–6.
29. Cheeley J, Sahn RE, DeLong LK, et al. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 2013;68:247–54.
30. Fox FE, Kubin M, Cassin M, et al. Retinoids synergize with interleukin-2 to augment IFN-gamma and interleukin-12 production by human peripheral blood mononuclear cells. J Interferon Cytokine Res 1999;19:407–15.
31. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798–812.
32. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001; 137:581–93.
33. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001; 19:2456–71.
34. Abbott RA, Whittaker SJ, Morris SL, et al. Bexarotene therapy for mycosis fungoides and Sézary syndrome. Br J Dermatol 2009;160:1299–307.
35. Ruzicka T, Lynde CW, Jemec GB, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol 2008;158:808–17.
36. Cattelan AM, Trevenzoli M, Aversa SML. Recent advances in the treatment of AIDS-related Kaposi's sarcoma. Am J Clin Dermatol 2002;3:451–62.
37. Coors EA, von den Driesch P. Treatment of 2 patients with mycosis fungoides with alitretinoin. J Am Acad Dermatol 2012;67:e265–7.
38. Kapser C, Herzinger T, Ruzicka T, et al. Treatment of cutaneous T-cell lymphoma with oral alitretinoin. J Eur Acad Dermatol Venereol 2015;29(4):783–8.
39. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713–22.
40. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29: 2598–607.
41. Humme D, Nast A, Erdmann R, et al. Systematic review of combination therapies for mycosis fungoides. Cancer Treat Rev 2014;40:927–33.
42. Thomsen K, Hammar H, Molin L, et al. Retinoids plus PUVA (RePUVA) and PUVA in mycosis fungoides, plaque stage. A report from the Scandinavian Mycosis Fungoides Group. Acta Derm Venereol 1989;69:536–8.
43. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578–81.
44. Singh F, Lebwohl MG. Cutaneous T-cell lymphoma treatment using bexarotene and PUVA: a case series. J Am Acad Dermatol 2004;51:570–3.
45. Papadavid E, Antoniou C, Nikolaou V, et al. Safety and efficacy of low-dose bexarotene and PUVA in the treatment of patients with mycosis fungoides. Am J Clin Dermatol 2008;9:169–73.
46. Whittaker S, Ortiz P, Dummer R, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). Br J Dermatol 2012;167:678–87.
47. D'Acunto C, Gurioli C, Neri I. Plaque stage mycosis fungoides treated with bexarotene at low dosage and UVB-NB. J Dermatolog Treat 2010;21:45–8.
48. Lokitz ML, Wong HK. Bexarotene and narrowband ultraviolet B phototherapy combination treatment for mycosis fungoides. Photodermatol Photoimmunol Photomed 2007;23:255–7.
49. Talpur R, Ward S, Apisarnthanarax N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2002;47:672–84.
50. Knobler RM, Trautinger F, Radaszkiewicz T, et al. Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. J Am Acad Dermatol 1991;24:247–52.
51. Duvic M, Lemak NA, Redman JR, et al. Combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1996;34:1022–9.
52. Tsimberidou A-M, Giles F, Romaguera J, et al. Activity of interferon-alpha and isotretinoin in patients with advanced, refractory lymphoid malignancies. Cancer 2004;100:574–80.

53. Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer 2007;109:1799–803.
54. Stadler R. Optimal combination with PUVA: rationale and clinical trial update. Oncology (Williston Park) 2007;21:29–32.
55. Tsirigotis P, Pappa V, Papageorgiou S, et al. Extracorporeal photopheresis in combination with bexarotene in the treatment of mycosis fungoides and Sézary syndrome. Br J Dermatol 2007;156:1379–81.
56. McGinnis KS, Ubriani R, Newton S, et al. The addition of interferon gamma to oral bexarotene therapy with photopheresis for Sézary syndrome. Arch Dermatol 2005;141:1176–8.
57. Foss F, Demierre MF, DiVenuti G. A phase-1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2005;106:454–7.
58. Dummer R, Beyer M, Hymes K, et al. Vorinostat combined with bexarotene for treatment of cutaneous T-cell lymphoma: in vitro and phase I clinical evidence supporting augmentation of retinoic acid receptor/retinoid X receptor activation by histone deacetylase inhibition. Leuk Lymphoma 2012;53:1501–8.
59. Kannangara AP, Levitan D, Fleischer AB. Evaluation of the efficacy of the combination of oral bexarotene and methotrexate for the treatment of early stage treatment-refractory cutaneous T-cell lymphoma. J Dermatolog Treat 2009;20:169–76.
60. Talpur R, Thompson A, Gangar P, et al. Pralatrexate alone or in combination with bexarotene: long-term tolerability in relapsed/refractory mycosis fungoides. Clin Lymphoma Myeloma Leuk 2014;14:297–304.
61. Illidge T, Chan C, Counsell N, et al. Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma. Br J Cancer 2013;109:2566–73.
62. Budgin JB, Richardson SK, Newton SB, et al. Biological effects of bexarotene in cutaneous T-cell lymphoma. Arch Dermatol 2005;141:315–21.
63. Lin JH, Kim EJ, Bansal A, et al. Clinical and in vitro resistance to bexarotene in adult T-cell leukemia: loss of RXR-alpha receptor. Blood 2008;112:2484–8.
64. Staels B. Regulation of lipid and lipoprotein metabolism by retinoids. J Am Acad Dermatol 2001;45:S158–67.
65. Lilley JS, Linton MF, Fazio S. Oral retinoids and plasma lipids. Dermatol Ther 2013;26:404–10.
66. Rodondi N, Darioli R, Ramelet AA, et al. High risk for hyperlipidemia and the metabolic syndrome after an episode of hypertriglyceridemia during 13-cis retinoic acid therapy for acne: a pharmacogenetic study. Ann Intern Med 2002;136:582–9.
67. Sherman SI, Gopal J, Haugen BR, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. N Engl J Med 1999;340:1075–9.
68. Sherman SI. Etiology, diagnosis, and treatment recommendations for central hypothyroidism associated with bexarotene therapy for cutaneous T-cell lymphoma. Clin Lymphoma 2003;3:249–52.
69. Larsen F, Jakobsen P, Knudsen J, et al. Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. J Invest Dermatol 1993;100:623–7.
70. Targretin [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals NA LLC; 2013.
71. Scarisbrick JJ, Morris S, Azurdia R, et al. UK consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol 2013;168:192–200.
72. Thomsen K, Molin L, Volden G, et al. 13-cis-retinoic acid effective in mycosis fungoides. A report from the Scandinavian Mycosis Fungoides Group. Acta Derm Venereol 1984;64:563–6.
73. Neely SM, Mehlmauer M, Feinstein DI. The effect of isotretinoin in six patients with cutaneous T-cell lymphoma. Arch Intern Med 1987;147:529–31.