Evaluation of Alitretinoin for the Treatment of Mycosis Fungoides and Sézary Syndrome

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Keywords

Alitretinoin · Mycosis fungoides · Sézary syndrome · Cutaneous T-cell lymphoma · Retrospective study

Abstract

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of cutaneous T-cell lymphoma (CTCL). There is currently no cure for CTCL, and treatment is aimed at limiting disease progression. This study evaluated the efficacy and tolerability of alitretinoin in CTCL management. **Methods:** A retrospective, multicenter study was conducted on CTCL patients treated with alitretinoin as a primary agent or in combination with standard therapies. **Results:** Forty-eight patients with MF ($n = 40$) and SS ($n = 8$) with a median age of 59.7 years (± 14.3) were eligible for study inclusion. Treatment response data were evaluated in 40 patients and safety in 42 patients. 40.0% of the patients had early-stage, 43.8% had advanced-stage CTCL, and in 16.7% of patients there was insufficient information for staging. 40.0% (16/40) of the patients achieved a complete or partial response, whereas 47.5% (19/40) achieved stable dis-

ease, 12.5% (5/40) had progressive disease, and there were no cases of disease relapses in responders. Both early and advanced stages of CTCL were responsive to alitretinoin as a primary or combined modality. Alitretinoin was well tolerated, and 64.3% (27/42) of patients did not report any side effects. The most commonly observed side effect was hypertriglyceridemia. **Conclusions:** This retrospective analysis supports the efficacy and safety of alitretinoin in clearing skin disease and preventing disease progression in CTCL as a monotherapy or in combination with standard therapies.

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Introduction

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of non-Hodgkin's lymphomas characterized by skin-limited infiltration of neoplastic T lymphocytes. Mycosis fungoides (MF) is the most prevalent type of CTCL, accounting for up to 65% of cases [1]. In MF, the disease course is indolent and mostly skin limited, with patch or plaque stage disease that can persist for years to

Fig. 1. Flow chart of the methods: overview of study procedure. MF, mycosis fungoides; SS, Sézary syndrome; ISCL, International Society of Cutaneous Lymphoma.

decades [2]. Skin-limited MF can evolve through the patch, plaque and tumor stages, and can infiltrate the lymph nodes, viscera and blood [2]. The overall 5-year survival for patch/plaque stage IB disease is 86% with worsening mortality upon upstaging. Systemic involvement portends worse prognosis, with the overall 5-year survival for nodal, visceral and organ involvement in stage IVB disease being 23% [3]. Sézary syndrome (SS) is a more aggressive subtype than MF and is classically viewed as a leukemic form of CTCL presenting with erythroderma [1].

No curative therapies currently exist for MF and SS. The goal of treatment is to mitigate disease progression and provide symptom control. Management of CTCL depends on the disease stage [1, 2]. In early skin-limited patch and plaque stage MF (stage IA, IB), topical treatments and phototherapy are the mainstay. In patients with widely distributed or recalcitrant disease, retinoids are one of the first-line systemic options [2, 4].

Retinoids are synthetic derivatives of vitamin A and are small, lipophilic molecules that bind to retinoic acid receptors (RARs) and/or retinoid X receptors (RXRs) in the nucleus [5]. The activated retinoid receptors modulate gene transcription in cellular pathways involved in immune regulation, cell proliferation and differentiation [6]. Isotretinoin and acitretin bind RARs, whereas bexarotene binds specifically to RXR, and alitretinoin binds both RARs and RXRs. Of the retinoids, only bexarotene is currently approved for the treatment of CTCL [6, 7]. In

Table 1. Patient demographics

Mean age at diagnosis ± SD, years	59.7±14.3
Sex, n/total (%)	
Male	30/48 (62.5)
Female	18/48 (37.5)
TNMB stage MF/SS, n/total (%)	
MF IA	9/48 (18.8)
MF IB	10/48 (20.8)
MF IIA	0/48 (0)
MF IIB	8/48 (16.7)
MF IIIA	2/48 (4.2)
MF IIIB	1/48 (2.1)
MF IVA	2/48 (4.2)
MF IVB	0/48 (0)
SS	8/48 (16.7)
Unknown	8/48 (16.7)

MF, mycosis fungoides; TNMB, tumor-node-metastasis-blood; SS, Sézary syndrome.

phase 2 and 3 clinical trials, bexarotene was effective in treating approximately 50% of patients with refractory or persistent early-stage of CTCL, and long-term retrospective studies have shown similar outcomes [8, 9]. However, bexarotene has a high frequency of adverse events and is not readily accessible in some countries such as Canada [8, 9].

A small, retrospective study of MF and SS treated with alitretinoin showed an improvement in skin disease with

Table 2. Concomitant treatment with alitretinoin

Median total therapies with alitretinoin (range)	2 (0–5)
Common combinations with alitretinoin, <i>n</i> /total (%)	
Single-agent alitretinoin	5/48 (10.4)
Topical corticosteroids	16/48 (33.3)
Topical corticosteroid and NBUVB	6/48 (12.5)
Topical corticosteroids and local radiation	1/48 (2.1)
Topical corticosteroids and local radiation and phototherapy	3/48 (6.3)
Topical corticosteroid and prednisone	2/48 (4.2)
Other combinations	15/48 (31.3)

NBUVB, narrow-band ultraviolet light B.

minimal side effects [10]. Larger studies are needed to determine whether alitretinoin is an effective and safe treatment option for MF and SS. We report a 5-year, nationwide retrospective review of 48 patients with MF and SS treated with alitretinoin monotherapy or in combination with other standard therapies across 3 academic centers in Canada.

Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000512484) (Fig. 1) [10, 11].

Results

Study Population

A retrospective chart review was conducted across 3 academic centers in Canada of 48 patients with MF (*n* = 40) and SS (*n* = 8) treated with oral alitretinoin (10–30 mg daily) monotherapy or in combination with standard therapies. Of the 48 patients screened, 40 and 42 patients had complete charts for analyses of treatment response and adverse events, respectively.

Patient Demographics

Table 1 summarizes the patient demographics. The mean age of diagnosis was 59.7 ± 14.3 years (range 24–89 years). The gender distribution was 62.5% males compared with 37.5% females. 39.6% (19/48) of patients had early-stage CTCL (IA: 18.8%, IB: 20.8%), whereas 27.1% (13/48) had advanced-stage disease (IIB: 16.7%, IIIA: 4.2%, IIIB: 2.1%, IVA: 4.2%), and 16.7% (8/48) of patients had SS. 16.7% (8/48) of the patients did not have sufficient information for staging.

Table 3. Response to alitretinoin (*n*/total, %)

Complete response	5/40 (12.5)
Partial response	11/40 (27.5)
Stable disease	19/40 (47.5)
Progressive disease	5/40 (12.5)
Disease relapse	0/40 (0)
Overall response	16/40 (40)

Disease relapse is the number of patients whose skin disease relapsed after obtaining a complete or partial response. Overall response is a composite measure of the complete and partial responses.

Treatment Modalities

The mean disease duration before the initiation of alitretinoin was 3 years (range 0.1–17 years). Patients received a median of 3 (range 0–9) treatment modalities prior to starting alitretinoin. While 10.4% (5/48) of patients received alitretinoin as a single agent, 89.6% (43/48) received alitretinoin in combination with other therapies (Table 2). The median number of concomitant treatments with alitretinoin was 2 (range 0–5). Adjunctive topical corticosteroids were most commonly prescribed with alitretinoin accounting for 33.3% (16/48), followed by adjunctive topical corticosteroids and narrow-band ultraviolet B radiation with alitretinoin accounting for 12.5% (6/48). 31.3% (15/48) of patients received alitretinoin with various combinations of interferon, methotrexate, extracorporeal electrophoresis, intralesional kenalog and/or other medical modalities (Table 2). The median follow-up was 14 months (range 2–75 months).

Response

The overall response, which is a composite of complete and partial response, was 40.0% (16/40). In particular, 12.5% (5/40) of patients achieved complete response

Fig. 2. Patient response to alitretinoin. Sixty-year-old female with MF (T2BNXM0) treated with alitretinoin 30 mg daily. **a** Initial patient encounter. **b** After 8 months of treatment.

Table 4. Adverse events

Outcomes, <i>n</i> /total (%)	
No observable adverse events	27/42 (64.3)
Observable adverse events	15/42 (35.7)
Adverse events, <i>n</i> /total (%)	
Hypertriglyceridemia	6/15 (40.0)
Diarrhea	2/15 (13.3)
Dermatitis	2/15 (13.3)
Headache	2/15 (13.3)
Fatigue	2/15 (13.3)
Back pain	1/15 (6.7)
Discontinued, <i>n</i> /total (%)	
Adverse events	7/18 (38.9)
Disease progression	6/18 (33.3)
Cost	5/18 (27.8)

without any documented disease relapse (Table 3). Of those with complete response, 3 patients had early-stage MF (2 with stage IA and 1 with IB), and 2 patients had advanced-stage MF (1 with IIB and the other with SS). 27.5% (11/40) had a partial response with 50–99% of skin clearance (Fig. 2). 47.5% (19/40) had stable disease, and 12.5% (5/40) developed progressive disease (Table 3). Five patients received alitretinoin monotherapy, and within this cohort, 1 patient had a complete response, another had a partial response, 2 patients had stable disease and 1 patient was lost to follow-up. When stratified by disease stage, the rate of complete response between ear-

ly-stage disease (IA–IIA) and advanced-stage disease (IIB–IVB, SS) was not significantly different ($p = 1.0$), albeit the study was not powered for this analysis.

Safety and Side Effects

The safety profile on alitretinoin was reported in 42 patients. Overall, alitretinoin was well tolerated, and 64.3% (27/42) patients had no reported side effects (Table 4). 35.7% (15/42) experienced at least one side effect with the most common being hypertriglyceridemia (40%), followed by diarrhea (13.3%), dermatitis (13.3%), headache (13.3%), fatigue (13.3%) and back pain (6.4%). There was no significant difference in the occurrence of side effects related to gender ($p = 0.5$) or disease stage ($p = 0.4$).

The rationale for alitretinoin discontinuation was reported in only 18 patients and of those patients: 38.9% (7/18) stopped due to side effects, 33.3% (6/18) discontinued due to disease progression and 27.8% (5/18) halted treatment due to cost (Table 4).

Discussion

When taken orally, retinoids are not considered immunosuppressive agents and therefore are an attractive option for the treatment of MF and SS [12]. Bexarotene has a response rate of approximately 50% but is not readily available in some countries including Canada [8, 9, 13]. Based on patterns of care across Europe and the USA,

bexarotene is one of the most frequently prescribed first-line treatments for CTCL especially in those with stage IIB disease [4]. However, the side effects associated with bexarotene are frequent, dose dependent and can lead to treatment cessation [8, 9, 14]. Other retinoids such as isotretinoin, acitretin and alitretinoin have been used off label for the management of MF with promising outcomes [6]. Therefore, consideration of other retinoids in treating MF and SS is warranted.

Like bexarotene, alitretinoin also targets the RXR but has a better safety profile, and many dermatologists have experience prescribing it for hand dermatitis and other dermatological conditions. Our retrospective study demonstrated alitretinoin is effective and relatively safe in treating MF and SS. The overall response, which is an aggregate of the complete and partial response, was 40.0% (16/40) in our study, and there were no reported cases of disease relapse following treatment. Our response rate was lower than a previous report showing an overall response rate of 90.9% in a retrospective study of only 11 patients [10]. Such differences are reflective of the variations in sample size and the institutional differences in prescribing. However, the overall response rate of 40% for alitretinoin is comparable to that of the phase II–III studies with bexarotene, which showed an overall response of 45–55% depending on the dose [9]. As a group, retinoids seem to be effective in treating about half of the CTCL patients, although randomized clinical trials and meta-analyses are needed to substantiate this observation.

Disease stage is an important consideration in treatment decisions for CTCL, as advanced stages can be more recalcitrant to therapy. The response to skin manifestations with bexarotene was observed across all TNM stages of CTCL [9]. In our retrospective study, 12.5% (5/40) of patients had a complete response with 3 patients with early-stage MF and 2 patients with advanced MF, 1 with stage IIB and the other with SS. Our findings suggest that like bexarotene, alitretinoin is efficacious in treating both early and advanced stages of CTCL. However, our study was not powered to stratify response rates with alitretinoin across all CTCL stages.

Retinoids have not been formally studied in combination with other treatments for CTCL, but bexarotene has been used off label in conjunction with extracorporeal photopheresis, interferon, phototherapy or other treatments [4]. Likewise, acitretin and alitretinoin have also been combined with other therapies, commonly skin-directed therapies for the treatment of MF and SS [10, 12]. Skin-directed therapies are used in both early stages of skin-limited disease and in later stages with systemic

therapies [8]. Consistent with previous reports, 89.5% (43/48) of patients in our study received topical corticosteroids alone or with other modalities such as narrow-band ultraviolet B radiation (Table 2). Other therapies also used in conjunction with alitretinoin included local radiation, extracorporeal photopheresis and interferon. The need for multiple treatment modalities likely reflects the difficulty clinicians have in managing the disease and that currently no cure for CTCL exists in our repertoire of medical options.

A major drawback of bexarotene is the high rate of adverse events that can lead to treatment cessation [8, 9]. Retinoids in general require monitoring of metabolic parameters such as triglycerides and cholesterol. In addition to these laboratory indices, bexarotene also requires close monitoring for anemia, neutropenia and hypothyroidism [9]. In contrast, alitretinoin is better tolerated than bexarotene; the most common adverse events for alitretinoin are hypertriglyceridemia, headache and cheilitis [15]. In this study, 64.3% (27/42) of patients had no observable side effects on alitretinoin. The most commonly observed adverse event was hypertriglyceridemia (Table 4). On average, increases in triglyceride levels can be expected in 30–44% of patients on acitretin, alitretinoin or isotretinoin, but is observed in upwards of 80% in patients on bexarotene which can precipitate pancreatitis [6, 16]. Fibrates and ω -3 fatty acids are options for lowering triglyceride levels in patients whose retinoid dosage cannot be reduced to maintain efficacy [17, 18]. Collectively, our findings are in agreement with a previous report demonstrating that alitretinoin is well tolerated in the treatment of CTCL [10].

Being a retrospective analysis, this study has several limitations. First, although the same data collection template was used across the study sites, there were some inconsistencies with the cohort and reporting of data. Second, only 10.4% (5/48) of patients received alitretinoin monotherapy, whereas most patients received alitretinoin in combination with standard treatments. Of those on alitretinoin alone, 60% (3/5) had a complete or partial response, 1 had stable disease and 1 was lost to follow-up. However, one third of patients received only topical corticosteroids with alitretinoin. Combination therapies are routinely utilized to treat CTCL, which reflects the complexity of a disease that requires multiple treatment modalities. Third, this retrospective analysis included patients with early and advanced stages of the disease, but our study was not powered to assess the efficacy of alitretinoin across the different stages of CTCL. The studies with bexarotene did not report efficacy stratified by dis-

ease stage either [8, 9]. We were also unable to comment on metabolic and laboratory monitoring parameters for patients on alitretinoin and to describe the adverse events in accordance with the common terminology criteria for adverse events. Overall, our retrospective review is in agreement with previous reports that alitretinoin is effective in the treatment of MF and SS, with few adverse events. Additional prospective and randomized studies with alitretinoin are needed to validate these observations.

Conclusions

Although bexarotene is used in Europe for the treatment of CTCL, it is not readily available in some countries such as Canada and has significant side effects that can lead to treatment cessation. Alitretinoin is effective and safe in the treatment of MF and SS and limits disease progression alone or in combination with standard therapies for early and advanced CTCL. Given its lower rate of side effects, alitretinoin appears to be a viable alternative in treating MF and SS.

Key Message

Alitretinoin is effective and safe in the treatment of mycosis fungoides and Sézary syndrome.

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Statement of Ethics

The patients in this paper provided written informed consent to publication of their case details. The study protocols were approved by the respective institute's committee on human research.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

T.T.V., R.A., R.G. and J.H. contributed to the development of the study protocol and were involved in drafting the manuscript or revising it for important intellectual content. N.A. and I.W.-W. analyzed and interpreted the data. L.S., J.-D.M.H. and J.C. assisted with protocol design, collected and analyzed data. S.W. and N.S. were involved in critical review of the paper and contributing to intellectual content.

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