

## Review Article

# Transitioning to Pegylated Interferon for the Treatment of Cutaneous T-Cell Lymphoma: Meeting the Challenge of Therapy Discontinuation and a Proposed Algorithm

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Cutaneous T-cell lymphoma (CTCL) is an uncommon non-Hodgkin lymphoma characterized by skin involvement, with the most recognized subtypes being mycosis fungoides (MF) and Sezary syndrome (SS). Interferon has been an established treatment for MF/SS since 1984 and is integrated into management guidelines internationally. In 2019, manufacturers abruptly discontinued interferon- $\alpha$ 2b and interferon- $\alpha$ 2a. Many alternative systemic therapies in MF/SS remain unfunded or unavailable in Canada, presenting a unique challenge. Although off-label use of pegylated interferon is a logical substitute, there are no established dosing guidelines and limited published experience. This case series provides a single-center experience on pegylated interferon- $\alpha$ 2b for treatment of MF/SS, a suggested management algorithm, and a review of the literature. All patients identified in the Calgary Cutaneous Lymphoma Program with stage IIB–IVB MF/SS treated with interferon- $\alpha$ 2b (4.5–9 MU/week) were switched to once weekly pegylated interferon (90  $\mu$ g, 0.5 mL) between February and July 2021. Response was monitored using the mSWAT and SkinDex-29 tools. Eight patients were switched to pegylated interferon, with a median disease duration of 69 months (range: 8–275 months). Five out of eight patients remain on pegylated interferon, with the remainder having switched to preplanned therapies. Two patients required dose reduction due to side effects, including grade II anemia and mood changes. The remaining patients had normal laboratory investigations and no additional side effects. Uncommon lymphomas like MF/SS have limited treatment options, and the impact of abrupt product discontinuation is substantial. We propose a management algorithm for the transition of patients from interferon to pegylated interferon.

## 1. Introduction

Cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin's lymphomas that arise in the skin and are of T cell origin [1]. The most recognized subtypes of CTCL include mycosis fungoides (MF) and Sezary syndrome (SS). MF is an indolent lymphoma of mature T cells that primarily affects the skin and makes up 60% of cases of CTCL. The clinical course often begins with patches that progress to plaques and eventually tumors over the course of years in a subset of patients [1]. SS, in comparison, is a leukemic form of CTCL that arises from thymic memory T cells and manifests with significant blood involvement, pruritic erythroderma, and

generalized lymphadenopathy. SS accounts for 2% of all CTCL cases [1]. The incidence of CTCL in the US between 1973 and 2002 has been 6.4–9.6/100,000 and is most prevalent in patients between the ages of 55 and 60, with a higher incidence in men than women [2].

Interferon (IFN) gained traction as a treatment modality for CTCL in 1984 and has since been integrated into CTCL guidelines internationally (Figure 1) [3–5]. Interferon is a naturally occurring cytokine that functions as part of the innate immune response to interfering with viral replication in addition to cytostatic and immunomodulating roles [6–8]. Recombinant interferons have been manufactured in three forms:  $\alpha$ -2a,  $\alpha$ -2b, and  $\gamma$ . IFN- $\alpha$ 2a and - $\alpha$ 2b have been

studied more extensively for the management of CTCL than IFN- $\gamma$ , with the difference between the two forms being a single amino acid that results from purification [8]. The immunomodulatory effects of IFN- $\alpha$  are beneficial in combatting immune dysfunction in CTCL by activating CD8+ T cells and natural killer cells to suppress an increase in Th2 activity that is typically mediated by malignant T cells in MF/SS [8]. Furthermore, IFN augments cytotoxic effects by increasing MHC class I molecules on lymphocytes and inhibits excess production of interleukin-5 and, subsequently, the proliferation of eosinophils (peripheral eosinophilia is associated with worse prognosis in the context of MF/SS) [8].

IFN- $\alpha$  is traditionally administered as a subcutaneous injection three times weekly at a dose of 3–6 million units (MU); however, a large range of dosing regimens have been reported in the literature for treatment of MF and SS [15–19]. In clinical use, lower doses at initiation ranging from 1 to 2 MU are useful to improve tolerance, particularly in individuals who are elderly or frail. Doses can be escalated gradually every four to twelve weeks as tolerated, as a full dose is more effective in achieving complete remission [20]. Acute side effects associated with IFN- $\alpha$  include flu-like symptoms such as fever, fatigue, chills, myalgias, arthralgias, and headaches. Adverse events associated with IFN- $\alpha$  are dose-related and often decline in severity over time. Other acute side effects include dose-related cytopenias. Chronic side effects include fatigue, decreased appetite, and weight loss [8]. Less common side effects include depressed mood and increased irritability, impaired cognitive function (more significant in the elderly population), cardiac arrhythmias, hypothyroidism and thyroiditis, altered taste, diarrhea, elevated liver enzymes, and rarely sensory disturbances. Interferon should be used with caution in individuals with preexisting autoimmune disorders and CD8+ cytotoxic T-cell lymphomas, as it may flare the underlying disorder [20].

In Calgary, IFN- $\alpha$ -2b subcutaneous (SC) injection was the standard of care for patients with mycosis fungoides and Sezary syndrome. However, IFN- $\alpha$ -2b was subject to product discontinuation by Merck citing “business reasons” in 2019 [12–14]. This sudden discontinuation highlights the fragility of treatment plans in the face of rare diseases like CTCL. As a consequence of IFN- $\alpha$ -2b discontinuation, patients treated with SC IFN- $\alpha$ -2b were transitioned to a pegylated IFN- $\alpha$ -2a formulation. Polyethylene glycol (PEG) as a drug adjuvant is well-established as it is an inert, water-soluble, and nontoxic modification that prolongs the clearance of proteins [21]. The addition of PEG to drugs such as IFN allows for the prolongation of serum half-life, such that dosing can be reduced to once weekly rather than three times weekly [22]. Pegylation offers the theoretical advantages of improved pharmacologic activity, prolonged half-life, improved safety and tolerability, increased patient adherence due to reduced toxicity, protection against enzymatic breakdown, improved solubility, and enhanced potency [21, 23]. These advantages, however, have not always been demonstrated clinically [24].

The current report will detail the experience with a series of eight patients for which the initiation of pegylated interferon (PEG-IFN) in place of IFN- $\alpha$ -2b was carried out from February to July 2021 due to product discontinuation. Additionally, a proposed management algorithm is presented. There are few publications assessing treatment outcomes with pegylated interferon in the forms of case reports and clinical trials [24–32]; therefore, a review of the literature assessing the efficacy of PEG-IFN for treatment of CTCL will be presented and discussed.

## 2. Materials and Methods

*2.1. Audit Program Database.* Patients in the Calgary Cutaneous Lymphoma Program actively treated with IFN- $\alpha$ -2b were identified from the program database, and records were obtained from their charts by LS and JH.

*2.2. Treatment Algorithm and Management Protocol.* All patients receiving IFN- $\alpha$ -2b were transitioned to 90 ug/week of pegylated interferon [33]. Patients were monitored for constitutional symptoms, including fatigue, chills, weight loss, and fever, in addition to any flu-like symptoms and mood changes. Complete blood counts, thyroid hormone levels, and liver enzymes (ALT, AST) were monitored to assess for thyroid or liver toxicity in addition to cytopenias and myelosuppression [33, 34]. A treatment algorithm is shown in Figure 2.

*2.3. Response to Date.* Treatment response was monitored by the modified severity-weighted assessment tool (mSWAT) and the SkinDex-29 survey. [35, 36] Time-to-next-treatment (TTNT) was calculated as the duration between the initiation of one treatment and the next line therapy [37].

*2.4. Literature Review.* On January 6<sup>th</sup> 2022, a search of Medline, EMBASE, and PubMed was conducted for publications referring to the treatment of cutaneous T-cell lymphoma (CTCL) with pegylated interferon using the search terms: (T-cell lymphoma OR T-cell lymphoma with an adjacency of 5 cutaneous OR mycosis fungoides OR Sezary syndrome) AND (pegylated interferon OR PEG-IFN OR Pegasys OR PegIntron). A total of 56 publications were retrieved from the EMBASE database, 5 publications were retrieved from PubMed, and 12 publications were retrieved from Ovid MEDLINE, which included ahead of print, in-process, in-data-review, and other nonindexed citations. Publications were included in the literature review if they met the following criteria: (i) referred to cutaneous T-cell lymphoma in the title or abstract and (ii) referred to the use of pegylated interferon for the treatment of CTCL upon full-text review. Review papers were excluded. Furthermore, while conducting full-text reviews, reference sections were searched to ensure all relevant literature were included. Publications were filtered based on language to include literature written in English. No other limits were imposed on the search strategy. A single reviewer independently

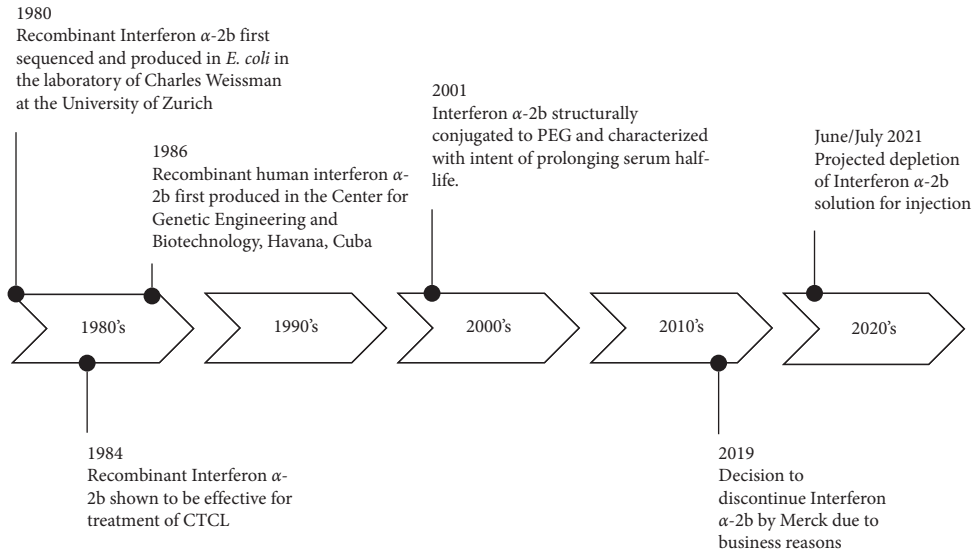


FIGURE 1: Timeline outlining the first sequencing and production of interferon- $\alpha$ -2b in Zurich [9], the demonstration that interferon is effective for CTCL treatment [4], human recombinant interferon- $\alpha$ -2b production [10], pegylation of interferon [11], and the discontinuation timeline [12–14].

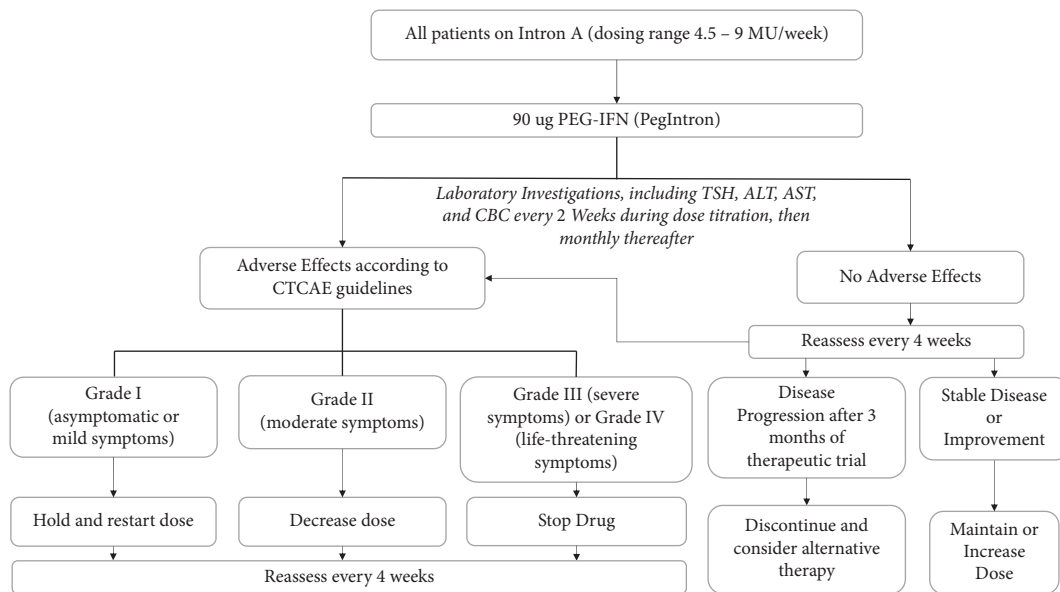


FIGURE 2: Management algorithm for the transition of patients with CTCL previously on interferon-alpha-2b to pegylated interferon.

reviewed the literature and extracted the relevant data from each publication (SO). A total of 9 publications were chosen for inclusion in the literature review according to the inclusion and exclusion criteria detailed above. One study used pegylated interferon in addition to an intralesional biologic, however, which was not included in the analysis as data from the pegylated interferon cohort were not separated from the cohort that received an intralesional biologic alone [38]. Results of each publication are specified in Table 1. An example of the search strategy employed for MEDLINE is demonstrated in the Appendix.

### 3. Results

**3.1. Patients.** After auditing all CTCL patients in the program (230 patients), eight were identified as receiving IFN- $\alpha$ -2b, with the total duration of interferon treatment ranging from 5 to 57 months. The IFN- $\alpha$ -2b weekly dose ranged from 4.5 MU to 9 MU, with all patients having been initiated on 9 MU (3 MU thrice weekly) of IFN- $\alpha$ -2b and doses modified based on the National Cancer Institute Common Terminology Criteria for Adverse Effects (CTCAE) [39].

TABLE 1: Summary of literature review of PEG-IFN treatment in CTCL.

Reference, year	n	Sex (♂, ♀)	Age (med, range)	Prior therapies	Combined therapies	Pathology diagnosis	Stage	Response	PEG-IFN dose	PEG-IFN treatment duration in weeks (median, range)	Reasons for discontinuation (if applicable)	Adverse effects	Outcome	Comments
Walker et al., 2021 [25]	7	4, 3	58, 38–79	TCS, topical nitrogen mustard, NB-UVB, local radiation therapy, total skin electron beam therapy, PUVA, TCS, IFN, retinoids	Phototherapy	5, MF	IIB or higher	1, CR 4, PR	1.5 µg/kg/week	10, 2–40	Disease progression, heart failure, neutropenia, infection	Constitutional symptoms (100% of patients)	Progression-free survival median, 3.5 months 6 dead	Patients had no previous interferon therapy. Study concluded that the dose of 9 µg/kg of PEG-IFN is too high and the clinicians employ a dose of 1.5 µg/kg
Schiller et al., 2017 [26]	6	5, 1	58.5, 48–74	PUVA, TCS, IFN, retinoids	None	MF	1, IA 3, IB 4, IA	2, CR 2, SD 4, CR 1, PR	180 µg/week	12		75% of patients experienced at least 1 AE Hematologic abnormalities, liver toxicity		One case of dose-limiting toxicity due to grade 3 elevation of liver enzymes. Dose-related increase in clinical response was not demonstrated
Hüsken et al., 2012 [24]	9	8, 1	58.75, 36–75	PUVA, TCS, retinoids	None	MF	2, IA 3, IB 2, IIA/ IIB 1, III 1, IV	1, CR 1, PR 1, SD	Intended 1.5 µg/kg/week Mean = 1 µg/kg/week (mean cumulative dose of 3562.2 µg)	42.9, 8–82	Disease progression (1), toxicity (2), 1 CTC grade, (3) depression, (1) exacerbation of psoriasis, one dose modification due to grade III constitutional side-effects	Constitutional, 77.8% Neuropsychiatric, 55.5% Gastrointestinal, 77.8% Hepatotoxicity, 77.8% Myelosuppression, 77.8%	Progression free survival 30.96 ± 4.9 months	Comparison between PEG-IFN + PUVA and IFN + PUVA showed overall response (CR + PR), which was higher in the PEG-IFN group (88.8% vs. 50%)
Fujimura et al., 2007 [27]	1	1, 0	60	PUVA, retinoids, intralesional IFN-γ	None	MF		CR	180 µg/week	2 years		None reported	Alive	
Yanagi et al., 2006 [28]	1	1, 0	67	TCS, PUVA, retinoids	Oral ribavirin, continued PUVA and retinoids for 4 weeks after initiation of PEG-IFN	MF	Plaque stage	CR	80 µg/week	4 weeks		None reported	Alive	Patient had chronic HCV infection, which was primary reason for initiation of PEG-IFN + ribavirin

TABLE 1: Continued.

Reference, year	n	Sex (♂,♀)	Age (med, range)	Prior therapies	Combined therapies	Pathology diagnosis	Stage	Response	PEG-IFN dose	PEG-IFN treatment duration in weeks (median, range)	Reasons for discontinuation (if applicable)	Adverse effects	Outcome	Comments
Fujimura et al., 2006 [29]	1	0.1	72	Total body electron beam therapy	None	CD8+ MF		CR after reinitiating PEG-IFN	180 µg/week	6 weeks	Liver enzyme elevation (ALT 165 IU/L), grade I	Hepatotoxicity		CD8+ MF was preceded by parapsoriasis en plaque
Patsiati et al., 2021 [30]	31	19.12	62.6	Not specified, PEG-IFN was 3 <sup>rd</sup> line treatment in 21 patients, 2 <sup>nd</sup> line in 8, 1 <sup>st</sup> line in 2	11, monotherapy with PEG-IFN 4, baroxetene 4, acitretin 4, MTX 8, topical chemotherapy	MF (26), folliculotropic MF (5)	5, IA 12, IB 1, IIA 7, IIB 3, III 3, IV	3, CR 14, PR 2, PD 11, SD 1, discontinued	135 µg/week (9) 180 µg/week (22)	Mean duration was 3.4 months prior to discontinuation in 9 patients. 8 reduced dose due to intolerance		Neutropenia (16), fatigue (9), anemia (4)		In cohort of 13 patients who switched from IFN-α-2a to PEG-IFN, 4 presented with fatigue and neutropenia
Lampadaki, 2021 [31]	1	0.1	70	PUVA + clobetasol Acitretin TSEC IFN-α MTX	Clobetasol, chlormethine gel	Folliculotropic MF	IB	PR	180 µg/week	Ongoing (as of publication)			Alive	The use of chlormethine gel was highlighted in this publication as an additional therapy for patients with stage IB and IIB MF who have failed previous treatment
Bakar et al., 2015 [32]	1	0.1	33	Local RT + total body NBUVB IFN-α	PUVA	MF	IA	PR	50 µg/m <sup>2</sup> /week	7.5 months ongoing (as of publication)			Alive	Case report of a patient with tumor-stage MF of the vulva treated with local RT followed by IFN and then transitioned to PEG-IFN

TCS, topical corticosteroids; NB-UVB, narrow-band ultraviolet B; MTX, methotrexate; IFN, interferon; PEG-IFN, pegylated interferon; CR, complete resolution; PR, partial resolution; SD, stable disease; PD, progressive disease; PUVA, psoralen + ultraviolet A; HCV, hepatitis C virus.

All eight patients were initiated on a once weekly subcutaneous injection of 90 ug (0.5 mL) PEG-IFN, with the exception of one (patient 8), who was initiated on 45 ug (0.25 mL) weekly. This was due to the absence of a specific dosing algorithm at the time. There were 4 males and 4 females included in the study. All the included patients were Caucasian. The median age of patients in the cohort was 68, ranging from 50 to 86. All patients had histologically confirmed CTCL ranging from stages IIB to IVB [1], with one patient demonstrating the folliculotropic subtype of MF and three patients having large cell transformation (LCT) on histopathology (Table 2).

After initiation of PEG-IFN treatment, one patient (patient 7) met the Grade II criteria for anemia and subsequently received a dose reduction to 45 ug weekly (0.25 mL). A second patient (patient 3) experienced mood side effects and received a dose reduction to 70 ug (0.4 mL) weekly. All other patients had normal blood counts and thyroid and liver function tests throughout the duration of treatment and had no additional side effects upon switching to PEG-IFN. Two patients were being treated for SS, while six patients were being treated for MF. Three of the six patients with MF had large cell transformation, and a single patient had folliculotropic MF. The stages of CTCL in the presented cohort ranged from IIB to IVB. Almost all patients except one were being treated with concurrent therapies including extracorporeal photopheresis (ECP), UVB phototherapy, topical carmustine 0.4% ointment, acitretin, imiquimod (3.75%), topical corticosteroids (5%), and systemic retinoids during both interferon and pegylated interferon treatment. Mogamulizumab was initiated as the next line of treatment in two patients, a decision that had been made prior to the initiation of pegylated interferon. In these cases, the switch to pegylated interferon was simply a bridging therapy between interferon and mogamulizumab. The time on pegylated interferon for patients 1 and 2 switched to mogamulizumab was 24 and 37 days, respectively. Patient 5 was similarly planned to initiate romidepsin under the same circumstances, with pegylated interferon as a bridging therapy for 4 months before romidepsin initiation. Patient 6 was initiated on total skin electron beam (TSEB) therapy in addition to pegylated interferon after 36 days on pegylated interferon alone. Clinical images prior to switching to pegylated interferon and after the switch are shown in Figures 3 and 4. We see that in Figure 3, the patient (patient 3) had relatively stable disease after initiation of PEG-IFN. This patient was further treated with home phototherapy, topical carmustine 0.4%, and topical tazarotene. Interestingly, this was a patient in whom the dose of pegylated interferon was stepped down due to adverse effects, and his subsequent mSWAT and SkinDex-29 scores were worse. The patient in Figure 4 (patient 4) had some improvement in disease with pegylated interferon, in addition to topical imiquimod 3.75% and oral acitretin. Therapies trialed prior to interferon are shown in Table 3.

**3.2. Literature Review.** A total of 66 cases of CTCL treated with pegylated interferon were included in the literature review through case series, case reports, and retrospective cohort studies (Table 1). Pegylated interferon was not often administered as monotherapy but rather was combined with phototherapy, psoralen plus ultraviolet-A radiation (PUVA), systemic retinoids, methotrexate, topical therapies (clobetasol, chlormethine gel, topical chemotherapy agents), and ribavirin (Table 1). Pegylated interferon has been reported for the treatment of Stage IA to IV CTCL. The most common starting doses of pegylated interferon reported were a combination of either weight-adjusted dosing of 1.5  $\mu\text{g}/\text{kg}/\text{week}$  or a flat dose of 180  $\mu\text{g}/\text{week}$ . Reasons for discontinuation of pegylated interferon included disease progression, heart failure, cytopenias, toxicity, mood changes, exacerbation of other skin diseases, and hepatotoxicity. The most common adverse effects experienced with pegylated interferon were constitutional symptoms, hematologic abnormalities/cytopenias, liver toxicity, GI symptoms, and neuropsychiatric symptoms.

#### 4. Discussion

Given the heterogeneity of the patients in the present cohort with respect to prior therapies, duration of interferon, duration of pegylated interferon, and concurrent therapies administered, it is difficult to ascertain the extent of CTCL response to the switch from interferon to pegylated interferon. However, we aim to outline our single-center experience with the product discontinuation of interferon and the impact on treatment. Of the eight patients that were switched to pegylated interferon after having been initiated on interferon due to product discontinuation, three patients were switched to a previously planned alternative line of treatment and five continued on pegylated interferon with no additional side effects than those initially experienced with the nonpegylated form. Interestingly, four of the eight patients had been on interferon as a prior therapy (Table 3) and then subsequently were reinitiated on interferon later on in their disease course. Interferon is unique in which it can be trialed multiple times, and failing treatment once is not a contraindication to initiating it again later in the disease course. One patient who continued on pegylated interferon had total skin electron beam therapy (TSEB) added. The dose of pegylated interferon administered was 90  $\mu\text{g}/\text{week}$ , which perhaps falls in the subtherapeutic dosing range when compared to the literature, and it would be reasonable to increase the dosing if tolerated by the patient. It would further be reasonable to suggest premedication with analgesics/antipyretics to mitigate flu-like symptoms that can be associated with interferon when initiating a switch to pegylated interferon. Once weekly dosing regimen with pegylated interferon is more convenient for administration compared to the thrice weekly regimen required for interferon. We have demonstrated a starting point for switching patients to pegylated interferon in light of the discontinuation of interferon- $\alpha 2\text{b}$  and interferon- $\alpha 2\text{a}$ .

TABLE 2: Patient demographics, clinical features, and outcomes.

Patient	Age at diagnosis	Pathology diagnosis	Stage	IFN dose/week (MU)	TTNT-IFN (months)†	PEG-IFN start dose/week (ug)	Concurrent therapies‡	mSWAT (baseline)	SkinDex-29 (baseline)	PEG-IFN current dose	Adverse effects	Next line of treatment	TTNT-PEG-IFN (days) §	Time on PEG-IFN (months)¶	mSWAT	SkinDex-29	Outcome	OS from diagnosis (years)
1	50	SS	IVB	6	8	90	ECP	84	72	—	—	Moga	24	0.8	80	62	Alive	1.2
2	66	SS	IVB	6	7	90	ECP, retinoids	90	11.6	—	—	Moga	37	1.2	90	11.6	Alive	1.0
3	60	MF, LCT	IIB	6	38	90	UVB, carmustine	3	59	70	Decreased mood	—	—	6	20	61	Alive	9.6
4	69	MF (folliculotropic)	IIB	4.5	19	90	Actretin, imiquimod, TCS	12	55	90	—	—	—	5	11	35	Alive	2.4
5	73	MF	IIB	9	21	90	UVB	80	52	—	—	Romi	128	4.3	60	76	Alive	13.6
6	67	MF, LCT	IIB	6	8	90	Isotretinoin	53.5	71	90	—	TSEB¶	—	5	26	—	Alive	5.4
7	86	MF, LCT	IIB	9	5	90	—	34	36	45	Grade 1 anemia	—	—	6	23	34	Alive	22.7
8	71	MF	IIIA	6	57	45	ECP, alitretinoin	NR	NR	45	—	—	—	5	27	—	Alive	7.9

†TTNT between interferon and pegylated interferon, ‡concurrent therapies during both IFN and PEG-IFN, § TTNT between pegylated interferon and the next line of treatment, if applicable, ¶ as of time of the publication, ¶¶ the patient was initiated on TSEB while remaining on PEG-IFN, initiated after 36 days on PEG-IFN. OS, overall survival; Moga, mogamulizumab; Romi, romidepsin; TSEB, total skin electron beam therapy; NR, not recorded



FIGURE 3: Clinical images from patient 3, prior to initiation of pegylated interferon (a) and after the switch (b).

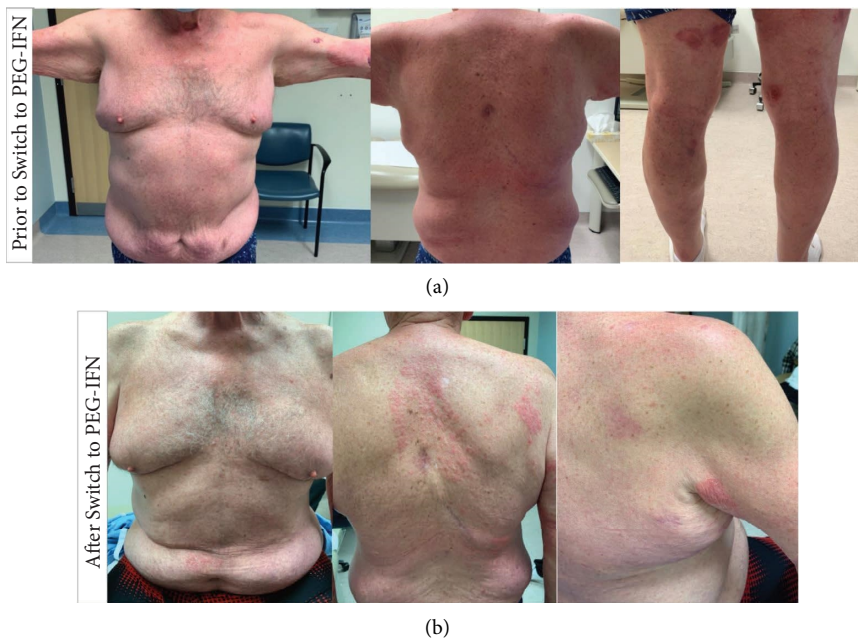


FIGURE 4: Clinical images from patient 4, prior to initiation of pegylated interferon (a) and after the switch (b).

TABLE 3: Prior therapies to interferon that were trialed in the presented cohort of patients.

Patient	Number of lines of treatment prior to IFN	Previously trialed therapies
1	1	TCS, ECP
2	1	TCS, ECP
3*	4	TCS, phototherapy (broad band), retinoids, radiation, methotrexate
4	3	TCS, phototherapy, retinoids, radiation
5*	9	TCS, PUVA, TSEB, methotrexate, nitrogen mustard, interferon (2014–2016), chemotherapy, bortezomib, isotretinoin
6*	7	TCS, phototherapy, chemotherapy, retinoids, brentuximab vedotin
7	5	TCS, PUVA, radiation, retinoids, imiquimod
8*	4	TCS, ECP, interferon (2016), retinoids (alitretinoin, isotretinoin)

\*Patients who received interferon before the course in which they were switched to pegylated interferon. TCS, topical corticosteroids; ECP, extracorporeal photopheresis; PUVA, psoralen + UVA; TSEB, total skin electron beam therapy; IFN, interferon.



Pegylation of pharmacologic agents has been cited as offering theoretical advantages of improved pharmacologic activity, prolonged half-life, improved safety and tolerability, increased patient adherence due to reduced toxicity, protection against enzymatic breakdown, improved solubility, and enhanced potency compared to their nonpegylated counterparts [21, 23]. There are no studies directly comparing PEG-IFN- $\alpha$  to IFN- $\alpha$  alone in the context of CTCL to highlight these advantages; however, a retrospective study by Hüsken et al. compared PEG-IFN- $\alpha$ -2b in conjunction with psoralen PUVA to standard IFN- $\alpha$ -2a plus PUVA in patients with CTCL [24]. This study found that ultimately, overall response to treatment (complete and partial remission) was higher in the PEG-IFN arm; however, there was a higher incidence of liver toxicity and myelosuppression, which contradicts the theoretical advantage of reduced toxicity with pegylation. With that said, the PEG-IFN group had a lower rate of constitutional side effects and a higher 5-year relapse-free survival rate (75%) compared to the standard IFN group (50%) [24].

Other studies comparing PEG-IFN and IFN- $\alpha$  alone have been done in the context of high-risk melanoma. A multi-center prospective randomized phase III trial done by Eigentler et al. compared overall survival, distant metastasis-free survival, and disease-free survival associated with the use of PEG-IFN- $\alpha$  compared to IFN- $\alpha$  in patients with resected cutaneous melanoma (stages IIA–IIIB) [40]. The major findings included no significant differences in distant metastasis-free survival, disease-free survival, or overall survival between the two interventions. The PEG-IFN $\alpha$  arm of the study had higher rates of leukopenia and elevation of liver enzymes, while quality of life (QoL) assessment was identical between the two groups across all domains (QoL assessment was done through SF-36 questionnaires at regular intervals over 24 months). Ultimately, it was concluded that PEG-IFN- $\alpha$ , despite the once weekly dosing, did not improve outcomes compared to IFN- $\alpha$  three times weekly, and a higher proportion of patients on PEG-IFN discontinued treatment due to toxicity [40]. Further work by Grob et al. compared PEG-IFN- $\alpha$ 2b and IFN- $\alpha$ 2b in the context of patients with melanoma and macrometastatic nodes. It was similarly found that there were no differences in outcomes between the interventions, with a higher risk of adverse events and discontinuation of treatment reported in the PEG-IFN- $\alpha$ 2b arm [41].

Rare diseases like MF and SS are at risk of abrupt product discontinuation, requiring a change in treatment planning. We have demonstrated a management algorithm for patients with CTCL who have been affected by the business decision of Merck to discontinue interferon production, involving a switch to the pegylated form. Pegylated interferon has been shown in the limited literature to be at least as good as or better than its standard counterpart; however, a potential limitation is that pegylated interferon is more expensive than its nonpegylated counterpart, which may preclude use in certain regions. Another limitation of the present analysis is the fact that all patients who transitioned to pegylated interferon were Caucasian, therefore making it difficult to ascertain the effects of race and ethnicity. The

management algorithm demonstrated here uses a lower dose of pegylated interferon than previously described in order to mitigate adverse events and discontinuation, and it is up to the clinician's discretion to use higher doses as have been reported in the literature (Table 1) and, if tolerated, increase dosing over time. Pegylated interferon can be used in combination with a variety of systemic treatments and modalities in addition to topical therapies, making it a versatile option for patients with CTCL (Tables 1 and 2).

## Appendix

### A. Search Strategy and OVID Medline Results

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review, and Other Nonindexed Citations and Daily <1946 to January 05, 2022> Search Strategy:

- (1) Exp T-cell lymphoma/(22080)
- (2) (t cell lymphoma\* adj5 cutaneous).tw, kf. (5957)
- (3) Mycosis fungoides.tw, kf. (6767)
- (4) Sezary syndrome.tw, kf. (2172)
- (5) 1 or 2 or 3 or 4 (24900)
- (6) (Pegylated adj3 interferon\*).tw, kf. (6565)
- (7) PEG-IFN\*.tw, kf. (2702)
- (8) Peginterferon.tw, kf. (2697)
- (9) PEGASYS.tw, kf. (141)
- (10) PEG Intron.tw, kf. (45)
- (11) PEG Intron.tw, kf. (36)
- (12) Pegylated interferon.mp. (6277)
- (13) 6 or 7 or 8 or 9 or 10 or 11 or 12 (9404)
- (14) 5 and 13 (12)

## Data Availability

The patient data used to support the findings of this study are restricted by the Health Research Ethics Board of Alberta in order to protect patient privacy. Data are available from Dr. Jori Hardin (jori.hardin@albertahealthservices.ca) for researchers who meet the criteria for access to confidential data.

## Ethical Approval

The research has been reviewed and approved on behalf of the Health Research Ethics Board of Alberta (HREBA)-Cancer Committee, effective July 7, 2022 (Ethics ID: HREBA.CC-22-0197).

## Consent

Written consent was obtained for clinical images.

## Disclosure

This paper has been presented as a poster presentation in the European Journal of Cancer <https://www.ejcancer.com/>

article/S0959-8049(22)00648-7/pdf, in addition to the Skin Research Group of Canada Conference.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

JH and LS conceived the presented work and anonymized patient data for data analysis, in addition to the review of the manuscript. SO completed the literature review, analysed data, and wrote of the manuscript. JC contributed to the review of the manuscript.

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