THERAKOS® Photopheresis Immunotherapy Overview

Mallinckrodt Pharmaceuticals

U.S. Indications: Cutaneous T-Cell Lymphoma (CTCL)

- The THERAKOS UVAR XTS® Photopheresis System/ THERAKOS CELLEX® Photopheresis System is indicated for use in the ultraviolet-A(UVA) irradiation, in the presence of the photoactive drug 8-methoxypsoralen (8-MOP), of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other forms of treatment.

- UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis System in the palliative treatment of the skin manifestations of CTCL that is unresponsive to other forms of treatment.

Target Audience, Market Size, Current Market Penetration

- Target audience: Academic Dermatologists and Hematologist/Oncologists
- Market size (incidence): ~32,000 CTCL patients in U.S. annually
  - 31% eligible for ECP therapy
- Current market penetration: ~11%*

*Based on 2012 IMS data

Efficacy of Extracorporeal Photopheresis (ECP) Monotherapy in the Treatment of Cutaneous T Cell Lymphoma

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Therakos Immune Cell Therapy

ABSTRACT

***Background*:** Mycosis Fungoides (MF) and its leukemic variant Sezary syndrome (SS) are disorders of malignant, skin homing helper/memory T-cells. MF presents with patches, plaques, or tumors, while SS presents with generalized erythroderma and blood involvement. Either can involve lymph nodes, blood, and viscera. A multi-center, open label, single arm clinical trial previously demonstrated the safety and efficacy of ECP as a monotherapy in the treatment of patients with advanced/refractory MF/SS (Edelson, et al, 1987, N Engl J Med, 316:297-303). The primary endpoint of this study was a ≥25% improvement in skin score maintained for at least 4 weeks. We present a long-term, secondary analysis of these patients to further evaluate clinical outcomes and predictors of response for ECP as a monotherapy in MF/SS. Partial (≥50%) and complete (≥90%) skin score responses, extent of skin disease, number of ECP treatments administered, and the time required to achieve 50% and 90% improvement in skin involvement were evaluated.

***Patients and Methods*:** Thirty-nine patients (pts) who met eligibility criteria were included in the secondary efficacy analysis as the intent-to-treat (ITT) patient population. Thirty-one pts with generalized erythroderma (GE) and 8 pts with extensive patch plaque (EPP) were treated with ECP on 2 consecutive days every 4-5 weeks for 3 months. No concomitant systemic medications for MF/SS were allowed on study; however, topical steroids could be applied to the hands and feet. Patients had received an average of 3.7 (range 0-13) prior therapies (systemic and topical). Immediately prior to undergoing ECP, all pts received oral doses of methoxsalen in order to achieve blood level concentrations ≥50 ng/mL. Skin improvement was calculated by comparing baseline skin score to skin scores on all subsequent treatment dates. The mean baseline skin score of the 39 ITT patients was 262 (median = 291) based on a maximum possible skin score of 400 points.

***Results*:** The median follow-up of the 39 ITT pts was approximately 4 years (range 9 days-7.8 years). Twenty-nine pts (74%) achieved at least a ≥50% improvement in skin score, and 16 pts (41%) achieved ≥90% improvement on ECP monotherapy. The type and extent of skin disease (GE vs. EPP) prior to the start of treatment did not predict response. Patients received a median of 12 (range 4-65) or 30.0 (range 12-109) individual ECP treatments to achieve a ≥50% or ≥90% response, respectively. The mean times to reach a ≥50% or ≥90% response were 8.4 ± 6 months (median=6.5) or 25.3 ± 14.9 mos (median=19.6), respectively. The mean duration of a ≥50% response was 32.5 ± 28.6 mos, which included a median of 20 (range 0-153) ECP treatments. Median survival from date of diagnosis and from date of first ECP treatment was 10.6 yrs and 5.4 yrs, respectively.

***Conclusions*:** In this long-term, follow-up analysis, ECP monotherapy was associated with a significant and durable improvement in skin score in the majority of patients with MF/SS.

Introduction

Cutaneous T Cell Lymphoma

- A broad spectrum of diseases mediated by skin-homing, malignant T lymphocytes
- This disease may progress from the skin to involve lymph nodes, blood, and visceral organs
- The most common, indolent form of CTCL is Mycosis fungoides (MF); the leukemic variant is referred to as Sezary syndrome (SS).
- MF may present clinically as plaques, patches, tumors, or erythroderma; whereas, SS is characterized by erythroderma with leukemic involvement with or without adenopathy or visceral involvement.
- Current treatment modalities for CTCL are not curative and do not offer effective means to prevent disease progression, provide durable remission, or improve quality of life for patients.

Extracorporeal Photopheresis (ECP)

- ECP involves the *ex vivo* exposure of methoxsalen-loaded peripheral blood leukocytes to UVA light (1.5 Joules/cm^2) using the UVAR Photopheresis System.
- In order to achieve blood level concentrations ≥50ng/mL, crystalline methoxsalen (.6mg/kg body weight) was orally administered to patients one and one half hours prior to the photopheresis procedure.
- 8-Methoxsalen binds to nucleic acid and irreversibly crosslinks DNA when activated by UVA to induce programmed cell death.
- Approximately 5-15% of total circulating white blood cells, or 5 X 10^9 leukocytes, are treated per ECP cycle.

From 1984 to 1992, Therakos, Inc. conducted a Phase III single arm, multi-center, open label clinical study to characterize the safety and efficacy of the UVAR™ Photopheresis System in conjunction with orally administered methoxsalen (8-MOP) in the control of skin lesions in CTCL patients. The primary endpoint was to determine the proportion of patients who exhibited a ≥25% skin score improvement maintained for 4 weeks after a course of ECP therapy. Due to advances in the evaluation criteria of CTCL patients and in the assessment of clinical responses, we initiated a retrospective data analysis of the original datasets from this study to determine the 50% and 90% response rates of CTCL patients to treatment with ECP monotherapy.

Purpose

The main objective of this study was to retrospectively analyze data from our original study in order to define the partial ≥ 50% and ≥ 90% skin score responses of CTCL patients to ECP treatments.

Methods

A. Patient Eligibility

- ✓ **Persistence of skin lesions consistent with CTCL and confirmation of diagnosis by (a) Histological analysis of skin lesion biopsies showing abnormal cells (b) Fluorescent antibody screening for T cell infiltration in skin lesion biopsies (c) Karyotype analysis and histological analysis of lymph node biopsy or (d) Peripheral blood smear showing abnormal lymphocytes.**
- ✓ **Use of prednisone for relief of itching was permitted on an individual basis only (≤10mg/day).**

B. Skin Score Evaluation:

- ✓ **Estimated Surface Area of each body section:** the body was divided into 29 anatomical sections weighted according to size
- ✓ **Body Area Severity:** obtained by rating the severity of skin involvement for each of body section using this 0 to 4 scale:
  - 0 - Normal Skin
  - 0.5 - Background of normal skin with scattered erythematous papules
  - 1 - Minimal erythema and edema; no scaling or fissuring
  - 2 - Substantial erythema and edema; no scaling or fissuring
  - 3 - Submaximal erythema, scaling, and edema; no fissuring or ectropion
  - 4 - Most severe; universal involvement with maximal erythema, edema and scaling; any fissuring or ectropion
- ✓ **Regional Score:** Body area severity score multiplied by the % surface area of that body section
- ✓ **Overall Skin Lesion Score:** sum of all regional scores

C. Study Design:

- ✓ **40 patients were enrolled at 6 different sites.**
- ✓ **Beginning in January 1984, patients were enrolled and continued to be treated over 3 years then followed for a maximum of 5 years.**
- ✓ **ECP therapy was administered as 2 back-to-back treatments delivered every 4-5 weeks for 3 months.**
- ✓ **Treatments could be accelerated in non-responders to 2 times every 2 weeks.**
- ✓ **Treatment of responders could be reduced to 2 treatments delivered each month until taper during maintenance periods.**

D. Patient Demographics (See Table 1):

- ✓ **39 pts completed at least one treatment and were included in the intent-to-treat analysis.**
- ✓ **31 pts had generalized erythroderma.**
- ✓ **8 pts had extensive patch plaque disease.**

E. Statistical Analyses:

- ✓ **The mean, standard deviation, median, minimum, and maximum statistics were used to summarize continuous measures.**

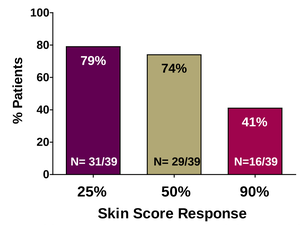
Table 1. Baseline Characteristics

Characteristic	All Patients (N = 39)
Age, years	
Mean	57
Range	24 to 80
Sex	
Men	28
Women	12
Length of Disease, years	1.4
Disease Classification	
Generalized Erythroderma	31
Extensive Patch Plaque	8
Skin Score, points	
Mean	262 out of 400
Median	291 out of 400
Total Time Followed in Study	
Mean	1309.4
Median	1394
Number of Prior Therapies	
Mean	3.7
Range	0 to 13
Mean 8-MOP Dose (mg)	54.12
Mean Hematocrit of Leukocyte-Enriched Blood	3.68%

Results*

I. Efficacy

A. Overall Response



B. Response by Disease Stage

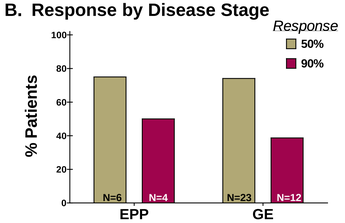


Figure 2. Skin Score Improvement. (A) Over the entire study, 79% of patients achieved a ≥ 25% skin score improvement, 74% of patients reached a ≥ 50% improvement (partial response) in skin score, and 41% achieved a ≥ 90% response. (B) Regardless of the initial diagnosis, both generalized erythroderma and extensive patch plaque patients responded similarly to ECP therapy.

II. Clinical Outcomes

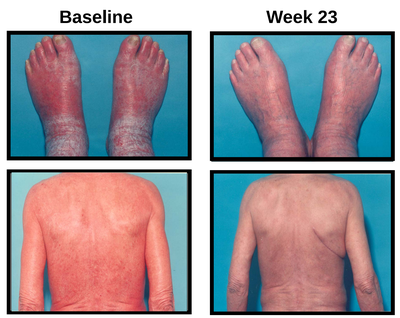


Figure 3. Photographs: Baseline and during treatment with ECP. Prior to entry into the study, this patient failed courses of steroids, accutane, and methotrexate; his baseline skin score was 382 (Classified as Generalized Erythroderma). After 23 weeks of ECP therapy, the skin on the feet of this patient shows decreased erythema and scaling; the toe nails show a reduction in thickening and less yellowing. On the back, there is a significant decrease in erythema and scaling. The skin score response at 23 weeks was reduced to 39 as this patient had a very significant response to ECP therapy.

III. Time to Response and Number of Treatments

Table 2 and Table 3 summarize the time to a 50% or 90% skin score response, respectively. The number of treatments required to achieve such responses is also shown.

Table 2. Time to 50% Response and Total Number of Treatments Required

	All Treated (N = 39)	Disease State GE (N=31)	Disease State EPP (N=8)
Number	29	23	6
Time to Response (months)			
Mean ± S.D.	8.4 ± 6	8.97 ± 6.53	6.28 ± 2.92
Median, range	6.5, (1.7 to 29.4)	6.5, (1.7 to 29.4)	6.4, (1.86 to 9.4)
Number of Treatments			
Mean ± S.D.	18 ± 13.56	19 ± 14.45	14.2 ± 9.47
Median, range	12, (4 to 65)	12, (4 to 65)	13, (4 to 31)

Table 3. Time to 90% Response and Total Number of Treatments Required

	All Treated (N = 39)	Disease State GE (N=31)	Disease State EPP (N=8)
Number	16	12	4
Time to Response (months)			
Mean ± S.D.	25.3 ± 14.9	25.7 ± 16.7	24 ± 9
Median, range	19.6, (6.9 to 62.8)	19.6, (6.9 to 62.8)	21.3, (17.1 to 36.4)
Number of Treatments			
Mean ± S.D.	40.6 ± 28.7	44.6 ± 32.1	28.5 ± 9
Median, range	30, (12 to 109)	33.5, (12 to 109)	28, (18 to 40)

Note: The standard deviations are large due to the fact that some patients were on study for extended periods while other patients were not (see median ranges)

IV. Duration of Responses

Table 4 and Table 5 summarize the amount of time CTCL patients maintained a 50% or 90% skin score response, respectively. The number of treatments received by patients during the maintenance period is also shown.

Table 4. Maintenance of 50% Response and Total Number of Treatments

	All Treated (N = 29)	Disease State GE (N=23)	Disease State EPP (N=6)
Amount of Time (months)			
Mean ± S.D.	32.5 ± 28.6	32.4 ± 28.9	33 ± 30.4
Median, range	21.7, (1 day to 81.9 mos)	19.6, (1 day to 80.3 mos)	35, (1 day to 81.9 mos)
Number of Treatments			
Mean ± S.D.	42.6 ± 48.28	44.7 ± 45.82	34.3 ± 60.93
Median, range	20, (0 to 153)	30, (0 to 144)	2.5, (0 to 153)

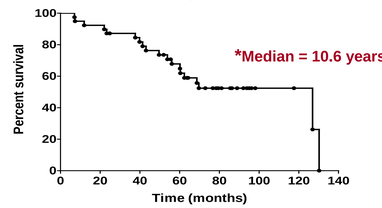
Table 5. Maintenance of 90% Response and Total Number of Treatments

	All Treated (N = 16)	Disease State GE (N=12)	Disease State EPP (N=4)
Amount of Time (months)			
Mean ± S.D.	18.3 ± 23.5	22.9 ± 25.7	4.68 ± 5
Median, range	8.9, (1 day to 76 mos)	378, (1 day to 76 mos)	3.7, (1 day to 11.2 mos)
Number of Treatments			
Mean ± S.D.	13.3 ± 17.55	15.4 ± 19.5	6.8 ± 8.54
Median, range	6, (0 to 64)	7, (0 to 64)	4, (0 to 19)

Note: The standard deviations are large due to the fact that some patients were on study for extended periods while other patients were not (see median ranges)

V. Survival

A. From Date of Diagnosis



B. From Date of First Treatment

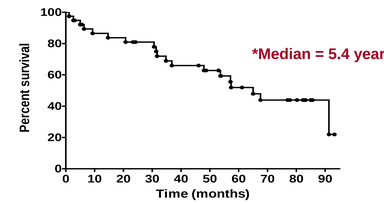


Figure 4. Survival Analysis was conducted using the 39 ITT patients. Deaths from all causes and patients lost to follow-up were considered, and survival was determined based on patient's date of death. Where date of death was not known or not applicable, the last known date of contact was used to calculate survival. *The median survival is a conservative estimate since 20 patients were censored at end of study. Because the percent of censored observations is over 50%, a reliable estimate of the median cannot be calculated.

Discussion & Conclusions

1. **Over the entire study period, 74% of CTCL patients treated with ECP monotherapy demonstrated a 50% improvement in skin score; 41% of patients demonstrated a 90% improvement in skin score.**
2. **Patients received a median of 12 (range 4-65) individual ECP treatments to achieve a ≥50% response; 30 (range 12-109) treatments were required to reach a ≥90% response.**
3. **The mean time to reach a ≥50% response was 8.4 ± 6 months (median=6.5); the mean time to a ≥90% response was or 25.3 ± 14.9 months (median=19.6).**
4. **The mean duration of a ≥50% response was 32.5 ± 28.6 months, which included a median of 20 (range 0-153) ECP treatments.**
5. **Median survival from date of diagnosis and from date of first ECP treatment was 10.6 yrs and 5.4 yrs, respectively.**

***Disclaimer: The data presented in the Results section have not yet been submitted to or reviewed by the FDA**

Single-Arm Study to Assess the Efficacy of UVADEX® (methoxsalen) Sterile Solution in Conjunction with the THERAKOS® CELLEX® Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft Versus Host Disease (aGvHD)

Background

- Hematopoietic stem cell transplantation (HSCT) is a curative option in children with high-risk malignancies.
- aGvHD is the major cause of morbidity & mortality after allogeneic hematopoietic stem cell transplantation. Systemic steroid treatment , 1st-line therapy for aGVHD, is associated with response rate of 30-60%.
- Steroid-resistant patients have poor prognosis with high transplant-related mortality (TRM). Several 2nd-line therapies have been proposed for management of unresponsive aGvHD, without proven beneficial effects on outcome or overall survival (OS).
- Even with use of standard GvHD prophylaxis, classical administration of ATG, calcineurin inhibitors & methotrexate, the incidence of chronic & aGvHD remains more than negligible.
- ECP has shown promising results as treatment for pediatric aGvHD, with direct impact on TRM rates & OS.
- A recent study of ECP in patients with aGvHD found that the 5-year progression-free survival of primary disease was 72% for responders (79%) & non-responders (30%) to ECP.

Purpose

- The purpose of this ongoing prospective study is to evaluate clinical utility of ECP in treatment of steroid-refractory pediatric acute GvHD.

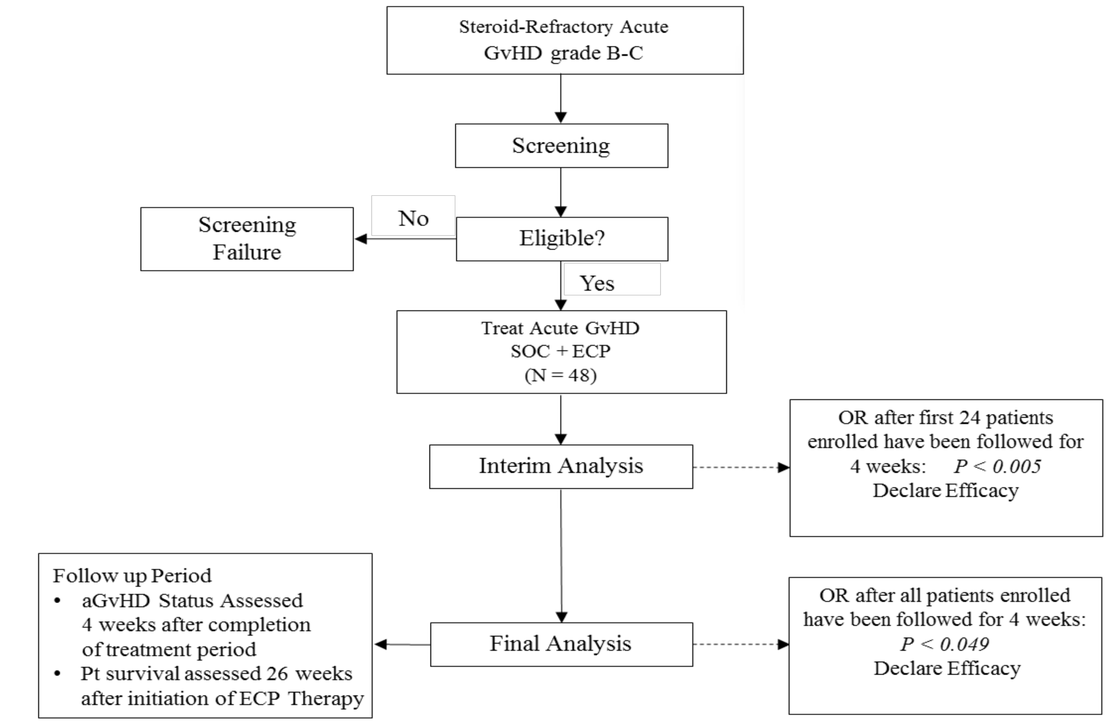
Objective

- The primary objective of this study is to evaluate the efficacy of extracorporeal photopheresis (ECP) in pediatric patients with steroid-refractory aGvHD.
- Secondary objectives are to assess the safety of ECP, duration of response to ECP, the steroid-sparing effect of ECP, and the organ-specific response to ECP therapy.

Study Population

- Male or female subjects ranging from 1 to 21 years of age.
- Steroid-refractory grade B-C aGvHD.
- Steroid-refractory is defined as progressive aGvHD within 3 days of, or no response within 7 days of starting systemic steroids at a dose of 2.0 mg/kg/day of methylprednisolone equivalents.

Study Design



Study Endpoints

Primary Endpoint

- The primary endpoint is the proportion of subjects who achieve an overall response (complete response [CR] + partial response [PR]) after 4 weeks (Day 28) of ECP treatment.

Key Secondary Endpoints

- The proportion of subjects who achieve an overall response 8 weeks (Day 56) after initiation of ECP treatment.
- Duration of response, defined as the length of time a patient maintains a response through Week 16 of the Follow-up Period.
- Proportion of patients who achieve an overall response after 4 weeks (Day 28) and 8 weeks (Day 56) of ECP treatment according to the modified Glucksberg criteria.