Intervally Collected Granular Safety Data Throughout Treatment with Polypodium leucotomos Extract for 56 days in 40 Adult Patients

Richard R Winkelmann, DO*, David E Cohen, MD, PhD**, Brian Berman, MD, PhD***, Mark S Nestor, MD, PhD****
*OhioHealth Dermatology Resident Physician; ** Professor of Dermatology, New York University School of Medicine; *** Professor Emeritus of Dermatology, University of Miami Miller School of Medicine and Co-Director, Center for Clinical and Cosmetic Research; **** Voluntary Associate Professor of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine and Director, Center for Clinical and Cosmetic Research

Polypodium leucotomos (PL) is a fern native to Central and South America that is widely available today as an extract (PLE) with versatile photoprotective and antioxidant properties.1 Historically, PL has been studied for its use in treating psoriasis, atopic dermatitis, vitiligo, melasma, and polymorphic light eruption. Basic science studies have demonstrated the antioxidant, immunoregulatory, and photoprotective effects of PLE but a knowledge gap regarding its safety profile is evident without prospective trials assessing its clinical and/or serological adverse events in human subjects over time.

A 2015 retrospective review outlined 19 human and 6 basic science studies in which oral PLE was administered at 120-1080 mg daily doses.2 No adverse effects were reported from PLE administration. In humans, mild-moderate side effects including gastrointestinal complaints and pruritus were found in a small composite number of patients (16/1016 [2%]). Overall, authors determined PLE was well tolerated and associated with a negligible risk of side effects. Recent Ames, murine, and clinical studies provide further evidence supporting the lack of treatment related adverse outcomes from PLE administration.4

A previously published randomized trial evaluating the photoprotective effects of PLE alluded to the clinical safety profile observed during the study. The purpose of this article is to further expand upon granular safety data collected during the trial in which patients treated with PLE were monitored interannually for serological and clinical adverse events.

Methods

40 healthy adult men and women between the ages of 18 and 65 years old with Fitzpatrick skin types I-IV were enrolled in the randomized prospective study. Subjects were excluded if they had an identified medical condition or were on a medication known to interfere with the primary objective of the study. Participants agreed to forego any skin procedures or treatments and women of childbearing potential used an effective form of birth control throughout the duration of treatment. Forty patients qualified and were randomized to receive 240 mg capsules of PLE twice daily (480 mg daily)(n=20) or placebo (n=20) twice daily for two months.

Vital signs, hematology, comprehensive metabolic panel, partial thromboplastin time (PTT), and prothrombin time (PT) international normalized ratio (INR) studies were performed at baseline and days 14, 28, and 56 of the trial. Statistical significance (defined as p<0.05) was measured using repeated measure NOVA methods for analyzing group difference of study outcomes over time. Additional subset analysis was performed in clusters grouped by age, gender, and skin type.

Results

Clinical Adverse Events

Patient #4-Control described one episode of sunburn. Two patients (Patient #10-Active and Patient #12-Control) reported symptoms of fatigue. Patient #28-Active and Patient #41-Active recounted mild GI discomfort/bloating symptoms. Patient #43-Active reported one episode of transient headache.

Vital Signs

Non-statistically significant weight change of >2 pounds from baseline was notable in three patients. Patient #7-Active and Patient #24-Active reported a weight gain of 10 pounds and weight loss of 9 pounds, respectively. Patient #5-Control lost a total of 51 pounds over the 56-day period.

Hematologic Studies

White blood cell (WBC) counts (normal: 4,500-10,000 WBCs/ml) from Patient #1-Control were elevated at baseline (12,000 WBCs/ml), normalized to 5,600 WBCs/ml on day 14, fell below the normal reference range to 2,400 WBCs/ml on day 28, and subsequently normalized again to 6,100 WBCs/ml at day 56. Patient #25-Active had transiently elevated WBC counts of 11,600 WBCs/ml on day 14 which increased from a baseline of 7,000 WBCs/ml. This abnormal WBC level in Patient #25-Active was not associated with clinical symptoms and was considered to be unrelated to PLE therapy.

Active patients (Patient #10-Active and Patient #24-Active) had elevated liver enzyme levels as AST and ALT in Patient #13-Active were 21 U/L and 27 U/L on day 14, 52 U/L and 83 U/L at day 28, to 21 U/L and 25 U/L at baseline, 1 U/L and 11 U/L by day 56.

Patient #39-Control had abnormal liver enzyme levels as AST and ALT in Patient #24-Active were 21 U/L and 20 U/L, respectively, completing the study with marginally elevated levels of 45 U/L and 54 U/L on day 56 despite values within normal limits on days 14 and 28. Patient #39-Control had abnormal liver enzyme levels as well and had the highest baseline weight of control group patients (255 pounds at baseline). Patient #39-Control’s liver enzymes increased from 23 U/L and 25 U/L at baseline, 21 U/L and 27 U/L on day 14, 52 U/L and 83 U/L at day 28, to 94 U/L and 90 U/L on day 56 for AST and ALT, respectively.

Over the course of the trial, no statistically significant variability was evident in serological studies commonly used by dermatologists to monitor for drug adverse events from test and control groups (all p>0.05). Additional subset analysis by age, gender, and skin type did not reveal statistically significant variance among groups over 56 days of PLE therapy (all p>0.05). Clinical side effects in the treatment group were mild, transient, and limited to bloating (n=2), headaches (n=1), and fatigue (n=1), all of which resolved by the end of the trial. No subjects withdrew from the study due to serious adverse events.

Mildly abnormal liver enzyme laboratory values were observed in one patient from the PLE treatment group and one study control subject and were not considered to be associated with treatment. All other reported abnormal laboratory values in hematoletic, metabolic, PTT, and PT/INR parameters were not associated with clinical symptoms and were considered to be unrelated to PLE therapy.

We report that PLE demonstrated a favorable safety profile in the doses studied for 20 adult treatment group subjects throughout 56 days of daily 480 mg PLE therapy. Most non-statistically significant differences in clinical laboratory parameters observed between test and control subjects were marginal in comparison to historical control ranges and were not considered to be associated with the treatment. Statistical analysis of serological data collected throughout the trial provides additional support for claims that PLE has a negligible risk of side effects. More studies may be required to better understand if there are any potential long-term clinical and serological effects of PLE therapy.

Acknowledgements

Funding for this study was provided by Ferndale Laboratories.

Drs. Winkelmann, Berman, Nestor and Cohen serve as consultants to Ferndale Laboratories.