Retinal Toxic Reactions Following Photopheresis

Jose Manuel Vagace, MD, PhD; Guillermo Gervasini, PharmD, PhD; Fernando Morais, MD; Julio Benitez, MD, PhD; Nieves Alonso, MD; Diego de Argila, MD; Isabel Arranz, MD; Roberto Bajo, MD, PhD

Background: Extracorporeal photochemotherapy (ECP), also known as photopheresis, is a generally well-tolerated therapeutic, immunomodulatory approach successfully used in cutaneous T-cell lymphoma and other diseases produced by T-lymphocytes such as graft vs host disease.

Observations: On 2 separate occasions, a 54-year-old white man with Sézary syndrome developed cutaneous phototoxic reactions and chorioretinitis after being treated with ECP. A pharmacokinetic study showed therapeutic blood levels of 8-methoxypsoralen as long as 18 weeks after therapy had been terminated. However, the analysis of mutations in genes involved in the drug’s disposition could not explain these abnormal levels.

Conclusions: To our knowledge, there has been no previous description of ECP-related retinal toxic effects. This adverse effect was probably linked to impaired drug elimination. Further studies would be needed to determine the underlying mechanism.

Arch Dermatol. 2007;143:622-625

E XTRACORPOREAL PHOTOCHEMOTHERAPY (ECP) or photopheresis is a therapeutic approach based on the biological effect of 8-methoxypsoralen (8-MOP) plus UV-A light on mononuclear cells collected by apheresis and reinfused into the patient. Photopheresis was first successfully used to treat cutaneous T-cell lymphoma and is now also used to treat T-lymphocyte mediated diseases. The treatment is generally well tolerated by the patient, with a low incidence of adverse effects, most of which are mild and transitory.

One of the reasons for the relative lack of clinical complications is the rapid elimination of the drug. It is known that cytochrome P450 (CYP) is involved because induction of this hepatic enzyme system leads to increased metabolism of the drug. Although the specific enzymes involved in 8-MOP metabolism are still unknown, there are indications that polymorphic enzymes such as CYP3A4, CYP3A5, or CYP2A6 could either be involved in the elimination of psoralen-type compounds or be inhibited by them. Psoralen has also been suggested to have an interaction with P-glycoprotein, a transmembrane protein encoded by the ABCB1 (MDR1) gene, which functions as a drug efflux pump and is involved in resistance to many anticancer therapies. Numerous polymorphisms and haplotypes have been described that can alter the expression and/or function of these genes and could therefore affect 8-MOP metabolism or transport.

We report herein a complication in a patient with Sézary syndrome who was treated with ECP and developed retinal toxic reactions. The case study showed unexplained, extremely durable levels of plasma psoralen.

METHODS

The patient authorized the scientific presentation of the data. The response to treatment was evaluated clinically by the Edelson skin score method, which quantifies the severity of the symptoms on a scale of 0 to 400 points. The percentage of lymphocytes with the characteristic pathological (CD3−, CD4+, and CD7−) phenotype was determined by quantitative flow cytometry.

PHOTOPHERESIS

We used a previously described ECP technique with minor modifications. Briefly, we used a Fresenius blood cell separator (AS.TEC-204, program PBSC-Ly; Fresenius AG, Bad Homburg, Germany) to collect 100 to 150 mL of mononuclear cell concentrate. The mononuclear cell concentrateuffy coat was adjusted to a constant volume of 300 mL by addition of isotonic sodium chloride solution and 3 mL of 8-MOP aqueous solution (Gerot Pharmazeutika, Vienna, Austria) to give a final drug concentration of 200 ng/mL. The buffy coat was transferred to a UV-A permeable bag (MacoPharma, Tourcoing, France).
and irradiated with UV-A under continuous shaking at 2 J/cm² for 15 minutes using a UV-A irradiator (UVAFEC) previously developed by our group. Finally, the resulting 8-MOP–photoactivated mononuclear cell concentrate was reinfused into the patient within 30 minutes. The effectiveness of the irradiation was evaluated by the response of the irradiated cells to phytohemagglutinin and by the flow-cytometric determination of cell viability (BrdU Flow Kits; Becton Dickinson & Co, Franklin Lakes, NJ).

This protocol was applied in biweekly cycles, each consisting of 2 procedures given on 2 consecutive days.

PHARMACOKINETICS

With the last ECP cycle administered, we monitored the psoralen plasma levels by high-performance liquid chromatography using the method described by Gómez et al. Ten samples from different patients receiving the same ECP protocol were used for comparison purposes.

GENOTYPING

In an attempt to determine the existence of gene polymorphisms that could affect psoralen disposition and hence at least in part explain the extreme durability of therapeutic blood levels of the drug observed in our patient, we tested for the presence of the commonest polymorphisms that affect the CYP3A4 and CYP3A5 genes in whites, namely CYP3A4*1B,12 CYP3A4*1F13 and CYP3A5*3,13 and for the existence of CYP2A6 functional variants (CYP2A6*2,14 CYP2A6*4,15 CYP2A6*5,16 and CYP2A6*9)17 using previously described techniques. Finally, the presence of the ABCB1 C1236T, G2677T, and C3435T allelic variants was determined by direct sequencing using a method developed in our laboratory.

A 54-year-old man diagnosed with Sézary syndrome was admitted to our hospital for ECP treatment. Physical examination showed generalized pruriginous erythroderma and axillary and inguinal lymph node enlargement. Laboratory evaluation showed leukocytosis (16.9 × 10⁹/L with 69% of Sézary cells in the blood smear), and normal hemoglobin level (16.6 g/dL) and platelet count (278 × 10⁹/μL). A characteristic T-lymphoma immunophenotype (CD3<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup>, and CD7<sup>−</sup>) was observed in 88% of lymphocytes and 42% of leukocytes. Skin and lymph node biopsies confirmed the diagnosis of cutaneous T-cell lymphoma, and rearrangements of the T-cell receptor γ chain gene were demonstrated in both biopsy specimens and in peripheral blood. The hepatic and renal biochemistry measurements and findings from the cardiovascular and ocular examinations were normal.

The patient underwent intensive treatment with photopheresis cycles initially accompanied by corticosteroid therapy. After the fourth cycle, the patient developed cutaneous phototoxic reactions following overexposure to sunlight. He had taken no other drugs or natural products that could explain this adverse reaction. One week after the fifth cycle, he presented abrupt bilateral loss of visual acuity (2/20 in both eyes). Ophthalmic exploration showed chorioretinitis, and findings from subsequent studies ruled out underlying pathologic conditions associated with uveitis. He was treated with methylprednisolone (250 mg intravenously every 6 hours for 5 days), which resulted in complete retinal healing and total recovery of visual acuity.

Given the good response of the lymphoma to the therapy, we decided to apply a further ECP cycle with absolute protection from UV-A radiation and observation of the psoralen levels. The monitoring revealed unexpected detectable concentrations of the drug long after its administration (Table). Four weeks after this treatment, the patient presented a new chorioretinitis, which again responded to high doses of corticosteroids. No further photopheresis was performed.

The Figure shows the aforementioned clinical complications and the patient’s response to therapy. The patient is presently receiving treatment with oral retinoids, the lymphoma is in remission, and the visual acuity is 10/20 OU.

Data from over 160 centers in Europe and the United States have shown ECP to have a very low adverse effect profile, and, to our knowledge, no cases of retinal toxic effects have previously been reported. However, our patient developed cutaneous phototoxic reactions and chorioretinitis after the fifth cycle of ECP. Chorioretinitis reappeared 4 weeks after a further ECP cycle, coinciding with unexpected measurable plasma levels of 8-MOP.

Psoralen may produce various eye injuries including corneal and lens opacities, conjunctival hyperemia, lessened tear production, and increased retinal photosensitivity. Chorioretinitis, however, has not been described. In general, avoiding exposure to sunlight is recommended for just 48 hours after each ECP cycle. In our patient, with such persistent drug levels, subsequent exposure to intense sunlight could have photoactivated the 8-MOP because the UV-A radiation is not completely filtered by the lens. Nonetheless, other mechanisms such as immune processes cannot be ruled out. Our ECP procedure is performed by adding 8-MOP directly to the mononuclear cell concentrate instead of oral administration. The amount of psoralen administered to a patient in this way is negligible, which explains why psoralen was not detected in the blood at any time in any of the 10 comparison ECP patients. The half-life of 8-MOP in blood following oral administration is approximately 1 hour. However, for our patient, the pharmacokinetic

<table>
<thead>
<tr>
<th>Table. Psoralen Plasma Levels Shown by the Patient After Receiving the Sixth Cycle of Extracorporeal Photochemotherapy (ECP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time After ECP</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>6 h</td>
</tr>
<tr>
<td>12 h</td>
</tr>
<tr>
<td>18 h</td>
</tr>
<tr>
<td>5 wk</td>
</tr>
<tr>
<td>18 wk</td>
</tr>
<tr>
<td>8 mo</td>
</tr>
</tbody>
</table>

©2007 American Medical Association. All rights reserved.
study carried out after administration of the last ECP cycle showed that he had measurable drug levels even 18 weeks later (Table). A psoralen blood concentration of at least 50 ng/mL and simultaneous exposure to UV-A radiation are needed for phototoxic effects to take place in tissue.21 With the dose used in every procedure of ECP (0.06 mg) and assuming total impairment of drug elimination, at least 5 procedures would be necessary to reach levels of 50 ng/mL in a patient weighing approximately 70 kg. Our patient manifested the first ocular toxic effect after the 10th procedure.

The detectable drug level at time zero following the final ECP cycle (40 ng/mL, Table) demonstrated the existence of drug accumulation during the former ECP pro-

Figure. A, Clinical complications of extracorporeal photochemotherapy (ECP): images of solar erythema and the first chorioretinitis episode; B, cycles of ECP and corticosteroid treatment; and C, clinical evolution of lymphoma evaluated by skin score and percentage of pathological phenotype lymphocytes. PK indicates pharmacokinetics.
cedures, which made us suspect the existence of an alteration in a metabolic route involved in the drug’s elimination. We tried to confirm this hypothesis by determining the presence of polymorphisms in drug metabolizing enzymes and transporters possibly involved in psoralen disposition. Of the CYP genes analyzed, the patient only carried the CYP3A5*3 allelic variant, which is present in more than 90% of the white population.22 He was also found to be heterozygous for 3 polymorphisms found in the P-glycoprotein—encoding gene ABCB1, namely C1236T, G2677T, and C3435T. While these mutations have been related to decreased P-glycoprotein functionality and subsequent drug accumulation and toxic effects,23 in our opinion it is unlikely that a heterozygous haplotype relatively common in the white population24 would lead to such an accumulation of 8-MOP as observed in the present case. Additional polymorphism, haplotype, and even phenotype analyses are needed to explain the extremely persistent drug levels in this patient.

In summary, to our knowledge, this is the first report of retinal toxic reactions resulting from ECP therapy. The mechanism of this adverse effect probably involves a genetic defect that seriously affects genes involved in 8-MOP metabolism or transport. Further studies should be undertaken to try to identify this defect and to determine whether it might be useful to explore this possibility before the implementation of photopheresis therapies to prevent similar problems in other patients.

Accepted for Publication: November 7, 2006.

Correspondence: Jose Manuel Vagace, MD, PhD, Department of Hematology, Infanta Cristina University Hospital, Avda Elvas s/n, E-06080 Badajoz, Spain (jvagacev@aehh.org).

Author Contributions: Dr Vagace had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vagace, Gervasini, Benitez, and Bajo. Acquisition of data: Vagace, Gervasini, Morais, Alonso, de Argila, and Arranz. Analysis and interpretation of data: Vagace, Gervasini, Morais, Benitez, Alonso, de Argila, Arranz, and Bajo. Drafting of the manuscript: Gervasini and Morais. Critical revision of the manuscript for important intellectual content: Vagace, Gervasini, Morais, Benitez, Alonso, de Argila, and Arranz. Administrative, technical, and material support: Gervasini, Morais, and Arranz. Study supervision: Vagace, Gervasini, Benitez, de Argila, Arranz, and Bajo.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grants P1020406 and 03/1432 from Fondo de Investigacion Sanitaria, Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Madrid, Spain, and Fondo Social Europeo; and grants SCS0502 from Junta de Extremadura, Consejeria de Sanidad y Consumo, Merida, Spain, and 2PR04A032 from Junta de Extremadura, Consejeria de Educacion Ciencia y Tecnologia, Merida.