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OPINION ARTICLE

Photopheresis*

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More than 1500 cases of patients treated by photopheresis have been reported in the world's medical literature since the initial publication by Edelson et al[1] of a multicenter trial of extracorporeal photochemotherapy in 1987 and—1 year later—the American Food and Drug Administration (FDA) approval of the technique in the treatment of cutaneous T cell lymphomas (CTCL). In this issue of *Actas Dermosifiliográficas*, Pérez-Carmona et al[2] publish a review of this therapy in CTCL, graft-vs-host disease (GVHD), and other conditions. In view of the limited number of randomized clinical trials, many colleagues remain unconvinced of the usefulness of this therapy. Furthermore, its use in conditions as distinct as lymphoma, prevention of rejection of solid-organ grafts, GVHD, scleromyxedema, scleroderma and other autoimmune diseases, nephrogenic systemic fibrosis, diabetes mellitus, and ulcerative colitis have led some authors to describe photopheresis as a "machine looking for a disease." Finally, many think that, given its high cost, there are other more efficient alternatives.

At present, in Spain, there is just 1 group in Hospital Universitario Ramón y Cajal where this technique is available. There also used to be one in Hospital Universitario 12 de Octubre, but the technique stopped being used because of difficulties in obtaining approval to buy the kits necessary for treatment, as well as the disillusion of the health care professionals responsible for managing patients with CTCL at the time (1).

The procedure includes 3 phases: leukapheresis, photoactivation with 8-methoxypsoralen and ultraviolet (UV) A, and subsequent reinfusion. The mechanism of action itself is not well known; in the case of CTCL, the procedure supposedly arrests the cell cycle of treated T cells and apoptosis occurs. These cells would then be phagocytosed by antigen-presenting cells with subsequent production of specific tumor-suppressor cells. In GVHD and other conditions, the mechanism of action is even less well established.

In the meeting of the European Organisation for Research and Treatment of Cancer (EORTC), held in Madrid in 2004, the different national groups presented and discussed best clinical practice with a view to arriving at a consensus for management of patients with CTCL. Photopheresis was included in the final document as a first-line recommendation for erythrodermic mycosis fungoides (MF) (with level of evidence 4, which was obtained from cases series and low-quality cohorts or low-quality case-control studies) and for Sézary syndrome (with level of evidence 2b, which was obtained from a randomized clinical trial deemed low quality because the follow-up rate was less than 80%).[3]

In that same meeting, the Spanish Lymphoma Group expressed its preference for the combination of chlorambucil plus prednisone for Sézary syndrome (but not for erythrodermic MF). That combination also appears (but in last place) in the list of first-line therapies recommended by the Cutaneous Lymphoma Group of the EORTC in the treatment of Sézary syndrome. The relative position of the different first-line treatments in the list gave rise to a degree of controversy with those responsible for drafting the final document. They decided the final order according to the preferences of the different national groups and the level of evidence available for the efficacy of the different therapies (2b for photopheresis and 4 for chlorambucil plus prednisone in Sézary syndrome).

The American National Cancer Institute (NCI) also included photopheresis in its guidelines for the management of stage III cutaneous lymphomas (as monotherapy) or stage IV disease (associated or not with other therapies).[4]

The reticence among different health care professionals towards photopheresis may be partly because it is really difficult to assess published studies given the differences in patient selection, photopheresis protocol, treatment duration, and, most importantly, response criteria. Bearing in mind all these limitations, the published mean response index (complete and partial) in the treatment of patients with CTCL is 63% (range, 40%-100%), with a mean

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(1) The author of this opinion article was not involved in the management of that team at the time, and was not directly implicated in this disillusion. However, he cannot rule out that his opinion is influenced or biased by the opinion of those who at the time were his teachers in dermatology.

complete response rate of 20% (range, 0%-62%). In dermatology, such response rates are often considered too low, although in the field of hematologic oncology, they are more than acceptable.

The Cochrane library does not include any reviews of photopheresis. British and Scandinavian groups, using a combination of systematic searches of best available evidence and expert opinions, have attempted to review the use of photopheresis, mainly for CTCL and GVHD.[5,6] These reviews included selection criteria, response criteria, a treatment guide, and a follow-up protocol.

In both reviews, the final recommendation for CTCL was that there is good evidence to support the use of the procedure in erythrodermic MF (stages III/IVa) and good evidence not to use it in nonerythrodermic MF. For combined treatments for CTCL, they concluded that there is moderate evidence for using photopheresis with interferon or total body electron irradiation. The remaining combinations (psoralen-UV-A or fludarabine) were assigned a lower strength of recommendation.

Nevertheless, the scientific community needs randomized trials to be performed. The Spanish Cutaneous Lymphoma Group would particularly welcome a trial comparing the technique with chlorambucil and prednisone.

We also need to find factors predictive of the outcome of this treatment. Dozens of patients with MF are being treated with photopheresis and there is no way of knowing a priori which patients are going to respond to therapy. It is essential to design genomics and proteomics studies with samples from patients before and during treatment to help us determine which patients should not be given photopheresis. Such studies could also yield important information on which drugs might be useful to overcome or reverse resistance to photopheresis.

The usefulness of photopheresis in GVHD is also subject to debate. The first publication was in 1994,[7] and likewise there appears to be little agreement on patient selection, treatment regimen, response criteria, or criteria for withdrawal of the treatment in the different papers published since then. Comparison of these papers is difficult given that assessment of outcomes in patients with GVHD is based on essentially subjective criteria with little laboratory data.

Most studies report a good response of skin lesions and liver dysfunction in GVHD, with response rates of around 65% and "complete responses" in between 30% and 100%. The response in patients with GVHD affecting other organs is limited or absent, but excellent responses have been reported in some cases.

As in CTCL, the best attempt at a systematic study of photopheresis in GVHD is that of Scarisbrick et al,[6] who aimed to limit photopheresis only to those patients who might obtain the most effective and efficient benefit possible. These authors assigned a strong level of recommendation to its use in patients with chronic cutaneous GVHD (not in acute disease), provided they are refractory or intolerant to corticosteroids or dependent on them.

In addition to randomized trials, it would also be useful to organize a single registry of patients undergoing photopheresis with common inclusion criteria, management, and response criteria. This would yield very useful information that would indicate which patients and in which conditions we should consider photopheresis. Likewise, in GVHD, there are no factors predictive of response to photopheresis. Translational research should be performed to detect a priori which patients may improve with this therapy.

Conflicts of Interest
The author acts as a consultant for MSD Spain for vorinostat and has also consulted at times for Ferrer S.A.

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