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EXPERT OPINION

Extracorporeal photochemotherapy: *past-it* or *promising*?

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Extracorporeal photochemotherapy has been used for almost three decades for the treatment of several T-cell-mediated diseases, and its efficacy has been proven in few well-designed controlled randomized trials. However, to date, there are no reliable data on a hypothetic dose-effect, optimal rhythm of administration, drug interactions, or the "pharmacokinetics" and "pharmacodynamics" of this cell therapy. In particular, it is not clear whether ECP gains to be used in combination with immunosuppressive or immunomodulative drugs. In the future, clinical trials may address these issues in order to clarify the most beneficial use of a cell therapy which absence of toxicity is uniformly recognized.

Keywords: apoptosis, immunotherapy, photopheresis, PUVA

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Extracorporeal photochemotherapy (ECP), also known as extracorporeal photopheresis, is a cell therapy that exploits the immunomodulatory properties of leukocytes that have been exposed *ex vivo* to ultraviolet light after a short incubation with a photosensitizing agent (psoralen). The original process was finalized by Edelson in the 1980s, and preliminary results published in 1987 for the treatment of cutaneous T-cell lymphoma [1] were strong enough to make ECP the first anti-tumoral immunotherapy to gain FDA approval, in 1988 [2]. Subsequently, its supposed anti-clonotypic effect directed against pathogenic T-cell clones and its excellent safety profile have prompted assessments of ECP in a multitude of T-cell-mediated diseases, with sometimes very encouraging but sometimes disappointing results (**Table 1**) [3-6]. Of note, ECP has never been proved to offer any survival advantage in a context of a randomized trial. Nevertheless, the fields of application of the procedure could be vast, and, for this reason, well-designed controlled trials, aimed not only at developing the clinical possibilities of the treatment, but also at evaluating its biological aspects, are desirable.

Indeed, due to its status as a medical device, ECP has never been assessed as rigorously as a new drug. Consequently, there are no reliable data on a hypothetic dose-effect, optimal rhythm of administration, drug interactions, or the pharmacokinetics and pharmacodynamics of this treatment where the active drug is an autologous cell (or more probably a set of autologous cells). In other words, Phase III and Phase IV studies have been completed yet we are still waiting for Phase I and especially a well-designed Phase II. For example, the only (nevertheless merit-worthy!) publication to address a hypothetic dose-effect results from a retrospective analysis and is thus subject to many unavoidable biases [7] and does not allow to distinguish a correlation from a causative relationship between efficacy and cell-dose. To date, the commonest regimen comprises one cycle (two daily consecutive sessions) a week or every other week. This schedule, like many other characteristics of ECP therapy (apheresis duration, blood volume processed, etc.), is really just force of habit and does not result from any reliable study.

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Table 1. Placebo-controlled randomized trials assessing ECP [3,4,8,14,15].

Date	Author	Indication	No. patients	ECP duration	Main results
2008	Flowers	Chronic cutaneous GvHD	93	3 months	Non-significant cutaneous improvement
2006	Knobler	Systemic sclerosis	64	12 months	Significant improvement of skin and joint involvement in patients with recent-onset scleroderma
2001	Bisaccia	Restenosis prevention after coronary angioplasty	78	16 weeks	Significant decrease in restenosis
2001	Ludvigsson	Onset of type 1 diabetes	49	12 weeks	Significant decrease in insulin requirements after 3 years
1999	Rostami	Multiple sclerosis	16	12 months	No significant effect

Table 2. Proposed mechanisms of action of ECP [10].

Generation of tolerogenic dendritic cells after uptake of apoptotic bodies
Alteration of cytokine profile
Reduced ability of APCs to stimulate T-cell responses
Enhanced production and function of regulatory T cells and T suppressor cells
Peripheral clonal deletion of effector T cells by activation-induced cell death

Many reasons can explain why a robust evaluation was never performed. First, as the treatment consists in infusing UVA-exposed autologous cells, there is little concern over "drug" intolerance or toxicity. Second, ECP was first proposed as a salvage therapy, thus exempting investigators from assessing the best risk–benefit ratio of this harmless well-tolerated treatment since the risk is virtually null. Indeed, the only limitation is patient acceptance or heaviness of the protocol, but rarely its toxicity. Third, in the late 1990s, several controlled randomized trials provided the evidence that ECP performs "better than placebo" in several conditions [5], yet in a number of these trials, the clinical efficacy of ECP was mild. As there would probably be less difference between two ECP regimens than between ECP and placebo, the number of patients to include in any Phase II trial designed to determine optimal rhythm of administration would be huge. In short, if ECP works and is well-tolerated, why spend so much time and money trying to do only slightly better?

The wider use of ECP in some desperate conditions taught us that the maximal effect of ECP can be long to manifest, in some situations taking months to appear. Note also that ECP does not bring an increase in infectious or other adverse events such as metabolic or organ-damaging effects. Hence, the drawbacks of ECP are immediate but its benefits are delayed. This characteristic distinguishes ECP from most other therapies, where the pitfalls lie behind a rapid benefit. The delayed action of ECP can in part explain why the results of clinical trials look disappointing in fields like GvHD where ECP is increasingly widely recognized as useful [8]. Indeed, given the impaired immune status in settings like GvHD, the ability of ECP to restore immune tolerance without increasing infectious risks makes it appear an especially desirable therapy.

Aside its excellent safety profile, the enigmatic mechanism of action of ECP is its second major strength, but also a weakness. Initially, it was thought that ECP was able to induce an antigen-specific tolerance through the principle of T-cell vaccination [9]. In fact, the immune effects of ECP rely on the behavior adopted by living cells (especially dendritic cells) when placed in contact with ECP-treated infused lymphocytes, which are known to enter an apoptotic process. Hence, it is likely that there is not just one but many mechanisms of action (**Table 2**) [10]. Moreover, it is reasonable to suppose that the effect of the infused cells depends on the anterior state of both the treated and the non-treated cells. We can further expect to see clinical findings (such as the correlation between immature B-cell populations and response to ECP [11]) led to the discovery of unsuspected mechanisms of action. This multiplicity of mechanisms can explain the apparent contradiction between the induction of immune reaction toward lymphoma cells and the induction of tolerance to allogeneic host, graft or auto-antigens. It will undoubtedly be exciting to learn the consequences of massive apoptotic cell infusion in a living organism, but for the time being at least, we are forced to continue accepting to use a therapy without precisely understanding how it works.

However, the lack of precise knowledge on the mechanisms underlying the action of ECP should become a serious issue in the era of monoclonal biotherapies. On top of evidence pointing to possible antagonism between the calcineurin inhibitor cyclosporine and the triggering of $CD4^+CD25^+$ regulatory T cells by ECP [12], the hypothesis of interactions between ECP and therapeutics directed against cells ($CD20^+$, $CD25^+$), cytokines (TNF, IL6) or other signaling molecules (BLyS, CTLA4) appears a solid one. As the place of ECP progressively evolves from a salvage therapy toward a combination therapy [8], the drug interactions issue will progressively become an even greater concern.

For all these reasons, the fascinating immunomodulatory therapy resulting from *ex vivo* combined exposure of leukocytes to sun and plant derivatives (psoralen was first

extracted from *Psoralea coryfolia*, but it also naturally present in fig trees, celery, parsley, and more) will necessitate further clinical evaluations to reach the minimal level of clinical knowledge required for any biotherapy. In the future, the use of less invasive procedures should facilitate the treatment while at the same time making it possible to settle on a relatively standard cell-dose [13]. Progress like this would not only facilitate treatment but also facilitate clinical evaluation. Until then, ECP must be scheduled as treatment on a case-by-case basis, thus justifying regular updates of the "state of the art" such as here in this issue of the journal.

Declaration of interest

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