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Lessons from the discontinuation of extracorporeal photopheresis

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Extracorporeal photopheresis (ECP) was initially used in the treatment of disseminated cutaneous T-cell lymphoma, with striking results including a significant response rate with minimal side effects [1]. This therapy involves collecting peripheral lymphocytes by apheresis, then treating these lymphocytes with 8-methoxypsoralen and exposing them to ultraviolet A light prior to reinfusion. The lymphocytes become apoptotic and are presented to CD4 T cells, which then leads to formation of regulatory CD4 T cells [2]. Many uses for ECP have been discovered, including treatment for mycosis fungoides [3], graft-versus-host disease [4], systemic sclerosis [5], and chronic lung allograft dysfunction (CLAD) [6].

Many practical questions exist regarding the application of ECP in these wide-ranging groups of patients. Timing of initiation of this therapy is often debated amongst clinicians across disciplines, who must weigh the risks of ECP, such as indwelling central venous access placement and substantial time commitment, with the potential benefits, which include some improvement in organ function and avoidance of further augmentation of immune suppression. Frequency of ECP treatments is another variable to be considered, with recent data suggesting that more frequent ECP can lead to better outcomes [7]. Whether ECP can be safely stopped, or if it can be discontinued without losing its beneficial effects, is unknown. Unfortunately, performing a prospective, randomized controlled clinical study to answer these questions definitively is not realistic, so we must rely on data acquired from well-selected cohorts to provide guidance in solving these problems.

In a current article in *Swiss Medical Weekly*, Dr Robinson and colleagues sought to provide guidance on the outcomes of patients with CLAD after ECP was stopped [8]. At this single transplant center, withdrawal of financial reimbursement forced the discontinuation of ECP in the majority of patients with CLAD at the end of 2014. For those clinicians who utilize ECP, difficulty receiving reimbursement is a common problem. Payers routinely cite a lack of high quality evidence, with only a single prospective study of patients with CLAD demonstrating benefit [9].

In this retrospective study of lung transplant patients with CLAD manifested as either bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS), the authors analyzed the outcomes of 12 lung transplant recipients for whom ECP was terminated in 2014. These patients had been receiving ECP for an average of 1001 days prior to its stoppage, with only four of them starting ECP within 12 months of discontinuation. The majority of these patients had BOS, with severe airflow obstruction and a median baseline forced expiratory volume in 1 second (FEV1) of 920 ml. During the 12 month lead-in period prior to ECP ending, this intervention had been successful in maintaining FEV1 stability, with a median FEV1 loss of 13 ml per month. This group of patients had been on stable doses of immunesuppressants, and none of the patients had escalation of corticosteroid dosing following ECP termination.

The authors report many notable findings following the discontinuation of ECP. First, there was a significant decline in airflow, with a median FEV1 of 800 ml obtained 6 months after stoppage. Second, 7 of the 12 patients died in the next 12 months: 3 from infection, 3 from progression of CLAD and 1 from a nonpulmonary malignancy. Those patients who died from infection also had progression of CLAD. Additionally, of the five patients who survived the first 12 months, two died from CLAD progression within 24 months after ECP was stopped, and another died from complications of repeat lung transplantation. Thus, of a stable cohort of patients receiving ECP for CLAD, only two of twelve survived 2 years after ECP was discontinued. The authors counter this cohort with a group of three patients who were able to resume ECP when the others had it discontinued. All of these individuals survived 2 years after the others had ECP stopped, with only one patient having a decline in FEV1 over this period.

Many limitations are presented by this manuscript. The small number of patients, retrospective nature, and lack of blinding or randomization make it difficult to draw definitive conclusions. However, the nature of the patients' underlying illnesses and confines placed on the clinicians by health insurance coverage make these issues nearly impossible to overcome. The mechanism by which these patients declined after the cessation of ECP is unclear, though a possible immunologic response with reduced generation of regulatory CD4 T cells is a consideration. It is also uncertain if immune suppression should have been augmented further after ECP cessation, and if this action might have prevented progression of CLAD, but with an increased risk for infection.

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The authors should be applauded for taking a difficult situation and using it to advance the study of this field by showing a possible association between withdrawal of ECP and mortality in patients with CLAD. This study should soothe concerns from payers that ECP is an effective therapy that improves outcomes in patients with CLAD, and is worth paying for.

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