

Annals of the Rheumatic Diseases

Leaders

Is there a future for extracorporeal photochemotherapy in the treatment of the rheumatological diseases?

The list of so called 'disease modifying agents' in rheumatoid arthritis now includes methotrexate and cyclosporin A. The efficacy of certain speculative treatments in the rheumatic diseases including antibody based therapies such as anti-tumour necrosis factor¹ and anti-ICAM,² cytokine toxic fusion proteins,³ oral administration of antigens,⁴ stem cell therapy,⁵ and cytokine receptor antagonists⁶ are being investigated. After the reported success of extracorporeal photochemotherapy (ECP) in systemically disseminated cutaneous T cell lymphoma⁷ in 1987 its benefits are also being explored in rheumatological conditions.

Technique of ECP

Two hours after oral methoxypsoralen, blood is removed from the patient, exposed to ultraviolet A light at room temperature, and then reinfused. This procedure can either be done as a continuous flow or by concentrating the lymphocytes and reinfusing as a bolus, and is usually performed on two consecutive days each month. In the initial group of 37 patients with therapy resistant cutaneous T cell lymphoma 27 improved with ECP, and over the past 10 years ECP has been adopted increasingly for this condition.

Mechanisms of ECP

Methoxypsoralen is a photoreactive agent that is temporarily transformed into its active form on exposure to ultraviolet A light before reverting in a fraction of a second to its inactive state. While ultraviolet A activated psoralens have a direct effect on intracellular DNA⁸ leading to cell death, this alone is unlikely to account for the pronounced reduction in lymphomatous T cells, as less than 10% of the blood lymphocytes are treated during each therapy. Other mechanisms responsible may include ultraviolet A exposed methoxypsoralen modification of leucocyte cell membrane DNA fragments, which are then taken up intracellularly⁹ and the inactivation of enzymes caused by methoxypsoralen modification of certain amino acid residues.¹⁰ None of the above actions, however, adequately explain the notable beneficial effects of ECP (table 1).

CD8+ T cells from patients with cutaneous T cell lymphoma have selective reactivity to the lymphoma cells, which are usually CD4+ and this can be improved by ECP.

Indeed, the presence of such CD8+ cells is a predictor for good response to ECP.¹¹ In a murine allograft rejection model, ECP treatment of T cells tripled the duration of skin graft survival with this tolerance being transferable by CD8+ T cells from the ECP treated mouse.¹² Such findings highlight the critical role of CD8+ T cells in this therapy.

HLA class I expression is increased by photoactivation of methoxypsoralen performed at room temperature, which are the conditions prevailing during ECP.¹¹ This raises the possibility that this increased expression may trigger or increase the CD8+ antilymphoma response. Normally such HLA class I molecules would contain bound antigen before their expression on the cell surface and in the event that they reach the membrane while still empty, are rapidly degraded at body temperature. However, leucocytes exposed to ECP express relatively large amounts of unfilled or 'empty' HLA class I on their surfaces, which could potentially be filled by small soluble peptides if they displayed the correct binding motif. Conceivably such peptides could be those released by pathogenic cells damaged by the ECP process including class I peptides themselves and therefore stimulate a class I mediated antilymphoma response. The temperature at which the ECP process occurs could play an important part in these phenomena as 'empty' class I is highly thermolabile at 37°C but stable at room temperature.¹³

ECP in rheumatological disease

In 1991 the first reported uses of ECP in the rheumatic diseases appeared. Since then only a limited number of further reports have been published.

In a pilot study seven patients with rheumatoid arthritis were treated with ECP on two consecutive days each month for three months then either monthly or biweekly for a further three months.¹⁴ Only a single minor adverse event was reported, and four of seven patients improved

Table 1 Possible mechanisms of action of ECP

Direct DNA effects
Modification of leucocyte cell membrane DNA fragments
Modification of amino acid residues causing enzyme inactivation
Increased HLA class I expression
Release of peptides including HLA class I by damaged pathogenic cells
Expression of 'empty' HLA class I with subsequent filling by soluble peptides

between 12 and 16 weeks in terms of both joint scores and counts. Some of the patients also recorded improvements in grip strength, walking time, and morning stiffness. Deterioration occurred two to three months after completion of ECP therapy. Unfortunately no further studies have been published.

A study of 10 patients with systemic lupus erythematosus (SLE) used a regimen of consecutive day ECP for two days monthly for six months then bimonthly for a further six months.¹⁵ Only eight patients completed the study, one leaving for personal reasons, another dying suddenly although no link with ECP was established. Seven had a significant clinical response to ECP with the group SLE activity index scoring system improving significantly over the period, with particular improvements being noted in skin lesions and arthritis. There was no concurrent improvement in laboratory parameters. It should be noted that all patients with cardiopulmonary or central nervous system manifestations or with serum creatinine >190 mmol/l were excluded from the study. A further report of two cases of SLE, one with urticarial vasculitis and the other with pemphigus foliaceus added ECP to their existing immunosuppressive therapy resulting in clinical improvement and enabling reduction or withdrawal of their other immunosuppressive therapies.¹⁶

In systemic sclerosis a randomised, parallel group, observer blinded clinical study has been performed in 79 patients comparing D-penicillamine with ECP.¹⁷ The latter was given for two consecutive days each month with evaluation at six and 10 months. While ECP produced statistically significant improvements in skin severity score, percentage skin involvement and oral aperture at both six and 10 months as well as hand closure at 10 months, the only statistically significant benefit over D-penicillamine was in skin severity score at six months. The ECP treatment was better tolerated by patients, however, and none of the ECP patients had to discontinue therapy because of side effects.

Eight inpatients with psoriatic arthritis received ECP treatment on two consecutive days at 0, two, and four weeks then four weekly until week 24 with psoralen-ultraviolet A irradiation being added from week 12.¹⁸ Four of the patients experienced considerable improvements in joint symptoms as determined by the Ritchie articular index, which lasted for over 12 months after the cessation of therapy and began within the first 12 weeks of therapy.

Comment

ECP seems to be a well tolerated therapy with established benefits in cutaneous T cell lymphoma. The precise mechanism of action remains uncertain, however, but intriguing hypotheses are now being tested. In the rheumatic diseases initial studies have indicated that ECP may be of benefit, however, large randomised placebo con-

trolled trials have yet to be performed. Comparisons with modern immunosuppressive regimens are also needed to determine the risk-benefit ratio. It is also of note that the cost of a given ECP session is in the region of £1000. So what is ECP? An apparently unproved, relatively expensive, novel therapy, which is available in only a few centres. Its role in helping unravel novel intricate mechanisms for targeting future therapies is likely to be its main contribution.

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