Acute graft v host disease: developing an extracorporeal photopheresis outreach service

Tracy Maher, Peter Taylor and Arun Alfred

ABSTRACT

Acute graft v host disease (AGVHD) is the main complication and cause of non-relapse mortality following allogenic hematopoietic stem cell transplantion. It occurs when donor immune cells attack host tissues. The three main organs that AGVHD affects are skin, liver and gastrointestinal tract, with one or more organs being involved. Extracorporeal photopheresis (ECP) is a second-line treatment for AGVHD in patients who fail to respond to high-dose steroids. It is an immuno-modulatory rather than immunosuppressive therapy. However, ECP is only available in a limited number of regional centres. This article describes how an ECP outpatient unit developed and implemented a fast-response ECP outreach facility for a referring hospital with the aim of improving access to treatment for this patient group.

Key words: Haematology ■ Stem cell transplantation ■ Immune response ■ Acutely ill patients ■ Service development

Acute graft v host disease (AGVHD) is a severe clinical condition that carries a high mortality rate (Greinix et al, 2000). It occurs as a consequence of stem cell transplantation, where donor immune cells damage the host tissues, particularly epithelial, hepatic and gut cells (Jacobsohn and Vogelsang, 2007). There are three main organs that AGVHD affects: the skin, liver and gastrointestinal tract, with one or more organs being involved. Symptoms can range from cutaneous blisters, severe abdominal pain, copious diarrhoea, persistent nausea and anorexia, to elevated bilirubin and abnormally elevated liver function test results and associated jaundice (Jacobsohn and Vogelsang, 2007). It usually occurs within the first 3 months after a transplant but can also occur later (Macmillan Cancer Support, 2014).

Tracy Maher, Photopheresis Nurse Specialist, photopheresis unit, The Rotherham NHS Foundation Trust, Rotherham, tracy.maher@rothgen.nhs.uk

Peter Taylor, Consultant Haematologist, photopheresis unit, The Rotherham NHS Foundation Trust, Rotherham

Arun Alfred, Consultant Haematologist and Director of Photopheresis Unit, The Rotherham NHS Foundation Trust, Rotherham

Accepted for publication: April 2018

Current first-line treatment for AGVHD is high-dose steroids (Macmillan Cancer Support, 2014). However, for patients who fail to respond to first-line treatment the prognosis is poor (Van Lint et al, 2006). Moreover, immunosuppressive treatments are associated with complications such as sepsis and viral reactivation (Martin et al, 2012). Also there is no clear consensus on the accepted second-line treatment for such patients and treatment is usually based on clinician preference, access to treatment, side effect profile and cost (Martin el al, 2012). In this setting, the use of extracorporeal photopheresis (ECP) provides for an immunomodulatory rather than immunosuppressive therapy with low toxicity and excellent safety profile (Alfred et al, 2017).

This article describes how an ECP unit developed and implemented a fast-response ECP outreach facility, with the aim of improving access to treatment for patients with AGVHD. These patients were unable to travel for this treatment, which is only available in a limited number of regional centres. There is no literature available regarding models of ECP outreach but various models of other outreach facilities do exist, from a solitary nurse to a multidisciplinary team approach, and have been widely used in community and social services for many years (Howard and Barnes, 2012; Marsh and Pittard, 2012). The aim of this article is to show that ECP outreach is a realistic alternative to providing it as an outpatient-only facility.

Extracorporeal photopheresis

'Extracorporeal' means blood outside the body and 'photo' means light. So in simple terms ECP is a light-activated blood treatment taking place outside the body. ECP has been used in the treatment of erythrodermic cutaneous T-cell lymphoma, chronic graft v host disease (CGVHD), selected diseases mediated by T cells, and solid organ transplant rejection (Hart et al, 2013).

ECP treatment is a cell-based immune-modulatory therapy and consists of anti-coagulated venous blood being drawn from a patient via a central line or peripheral venous access into the ECP machine where it is separated by centrifugation. The system is 'closed', in that blood and components are always retained in the system and are never separated from the device or patient until completion of the therapy. The patient is connected to the machine for approximately 2 hours for each treatment. Only

a portion of the circulating blood volume is removed (around. 10–15%) and on completion of the treatment all blood will have been returned to the patient.

During treatment the patient's blood is separated into components and the red cells and plasma not required are returned to the patient after each cycle. Leucocytes (or buffy coat) are isolated for further treatment. The leucocyte fraction is collected in a treatment bag integral to the ECP machine. A treatment dose of intravenous methoxsalen solution is calculated based on processed volume and injected into the treatment bag. The cells are then pumped through the light system within the machine where they are exposed to ultraviolet (UVA) radiation (photo-activation). Once completed the cells are returned to the patient.

During photo-activation the methoxsalen binds to the leucocyte fraction and on returning to the patient this induces apoptosis and up-regulates the antigen-processing ability of monocytes. These effects contribute to dampening down the over-productive immune response (Bladon and Taylor, 2005).

This treatment carries the minimal side effects of photosensitivity to the eyes and skin, possible vasovagal episodes (which can be counteracted by giving a bolus of intravenous saline) and a slight increase in skin erythema and pruritus. These are discussed and explained to the patient prior to treatment with the appropriate advice. The aim is for the immune-modulatory effect of ECP to allow tapering of steroid dosage without flare of GVHD symptoms and to eventually achieve complete steroid reduction.

The use of ECP in the treatment of CGVHD and AGVHD is well documented. It has been used effectively for over 20 years in the treatment of both of these conditions (Alfred et al, 2017). Knobler et al (2014) also highlighted the clinical efficacy of ECP but stated that the lack of randomised controlled trials meant that ECP results cannot be evaluated and ranked against other second-line treatments; however, the ability to decrease corticosteroids while receiving a course of ECP is reported as a significant and consistent criterion for ECP response.

ECP schedule for outreach AGVHD

ECP treatment for AGVHD is given on two consecutive days weekly for 8 weeks—this constitutes one cycle of treatment. Progress is monitored regularly with clinical and laboratory evaluation. Provided there is no evidence of deterioration treatment is continued for at least 8 weeks.

The treatment is performed by a trained machine operator with a nursing background who has competence in venous access, an understanding of the haematology patient, and who has completed a training course under the guidance of the ECP machine manufacturing company training technicians.

Evaluation of treatment response

Response to treatment is based on clinical evaluation of skin involvement, volume of diarrhoea and liver function tests. There is a concurrent aim during treatment to reduce the systemic steroid dose, thereby minimising as far as possible the immunosuppressive effects of this intervention.

The patient is assessed every day by the on-site haematology medical team followed by weekly teleconference calls to the ECP consultant to discuss medication adjustment and progress. The patient is also discussed at a weekly ECP multidisciplinary team meeting between ECP nurse specialist and consultant.

Development of the ECP outreach service

The rationale for the development of this service arose because of the increase in demand for acutely ill patients to be treated with ECP and the difficulties associated with the traditional outpatient setting. Patients with AGVHD generally need inpatient treatment as they are acutely unwell and cannot be treated in an outpatient setting, as is the usual approach in patients with CGVHD. Furthermore the patient with AGVHD may need treatment away from the transplant ward, such as in an intensive care setting. The principle of outreach treatment was to deliver the treatment at the patient's bedside in the most suitable clinical environment.

Initial attempts were made to treat these patients in the outpatient setting but their symptoms, such as urgency for defecation or micturition, lethargy and severe jaundice made

Table 1. Development of the ECP unit

Prior to 2013	Post 2013
■ 1 unit manager (full-time) ■ 3 qualified nurses (1 full-time, 2 part-time) ■ 1 healthcare assistant ■ 2 haematology/ECP consultants (one who is clinical lead) both on-site ■ No waiting list ■ 1 therapy room accommodating 4 patients	■ 1 unit manager (full-time) ■ 5 qualified nurses (3 full-time, 2 part-time) ■ 1 healthcare assistant ■ 2 haematology/ECP consultants (one who is clinical lead) both on-site ■ Service manager ■ No waiting list ■ 2 therapy rooms, 1 therapy room can be used for isolation patients
Treatment schedule: Session 1 8.00–12.00 Session 2 12.00–16.00	Treatment schedule: Session 1 07.30–10.30 Session 2 11.00–14.00 Session 3 14.30–17.30 ■ 4 patients in session 1 and 2 ■ 3 patients in session 3
An outreach referral was accepted and planned into rota on a weekly basis	When an outreach referral is accepted it is planned into the staff rota and patient treatment diary in advance for 8 weeks
Acceptance of an AGVHD referral from local hospital required ■ Removal of therapy chair ■ A bed placing in this area ■ 2-person ambulance crew ■ 1 nurse escort ■ 4-hour wait for collection	
Minimum staffing levels: 1 nurse to treat 2 patients 1 healthcare assistant to cover 08.00–16.00 1 unit manager	Minimum staffing levels : 1 nurse to treat 2 patients 1 healthcare assistant to cover 08.00–16.00 1 unit manager

Table 2. Clinical requirements to proceed with ECP

Venous access device required for ECP	A venous access device for ECP treatment must be a catheter that is able to withstand the negative pressure of the peristaltic pressure pumps without collapsing, and must provide a flow rate of at least 15 ml/minute, either : ■ A placed 16-gauge venous cannula in the antecubital fossa ■ A placed tunnelled central venous catheter capable of drawing off at least 15 ml/minute designed for long-term apheresis
ECP exclusion criteria (refer to ECP consultant)	Blood parameters: Platelet count less than 20 x 10^9/litre, haematocrit less than 0.27 (proportion of 1)
	Weight less than 40 kilograms
	Patient-specific: ■ Temperature of 38°C or above ■ Sepsis ■ No venous access ■ Unable to flush/aspirate venous central line ■ Active bleeding

it extremely challenging to protect their privacy and dignity while in the same treatment bay as the other day-case patients. Before the outreach service was implemented the patient would be transferred to the unit by ambulance and nurse escort with their medical notes, medications and in some cases ongoing intravenous infusions. The outpatient treatment area would therefore require alteration—the therapy chair needed to be removed and a bed made available.

If the patient required isolation then a single-occupancy hospital cubicle bed would have to be booked and on completion of treatment the room that the isolated patient used would then have to be terminally cleaned. Following treatment, the patient would then have to wait for 1–4 hours for ambulance transport back to the referring hospital. It therefore made much more sense to send the ECP machine and an ECP nurse specialist with the necessary equipment to the patient at the referring hospital.

Originally, in 2013, the ECP treatment bay consisted of four separate treatment areas, each with a curtain facility to afford some privacy, and whenever possible it was planned that the patient would attend the ECP unit when fewer outpatient visits were booked in, but this could not be guaranteed. The capacity for the ECP unit in 2013 was 8 patients per day, however, following expansion in 2014 there is now capacity for 11 patients on site and 2 patients off site (*Table 1*).

Preliminary meetings to implement the service

In July 2013 the ECP team reviewed the service for AGVHD patients who had been referred for treatment from the local tertiary hospital and decided that a significant improvement would be to provide an outreach service for them. The ECP team consists of two haematology/ECP consultants, one of whom is clinical lead. The ECP consultants have regular contact with the tertiary ward which is the leading haematology stem cell transplant centre for the region. This hospital is 7 miles away from the ECP unit. Patient selection for ECP requires assessment and then classification by a haematology consultant using the US National Institutes of Health GVHD global score (Jagasia et al, 2015). If the patient meets the criteria for ECP a referral is sent and processed.

Initially a service level agreement and contract had to be completed by the administration departments of both hospitals. Following this, the lead ECP nurses and ECP consultant had a planning meeting with the referring hospital consultants, lead nurses and hospital governance operatives. Issues discussed as important to the continuity of the service were:

- Governance issues: service level agreement, honorary contracts, referral of the patient, taking of consent to treat, standard operating procedures (SOPs) and the assessment of patient criteria for ECP
- ECP consultant would travel to the patient at the tertiary hospital and take consent; if this was not possible consent should be taken by the haematologist on the tertiary ward
- ECP consultant would arrange a teleconference with the tertiary unit consultant, to plan a treatment schedule for the patient with AGVHD.
- Familiarisation and induction of the ECP nurses to referring hospital
- Carriage and storage of equipment, safe disposal of equipment and blood products following treatment
- Telephone handover of patient from ECP unit to the outreach facility
- Duty rota and patient scheduling
- Transportation of ECP nurses to the outreach facility
- Education of ward staff on the requirements to treat the ECP patient
- Assessment of the quality of service at 6 months.

The ECP nurses then met with the nursing and medical team on the ward to explain the service and the procedure that would follow once a patient was referred for ECP. This included the patient's pre-procedure requirements for ECP such as referral, consent, haemodynamic stability, venous access requirements and the patient's blood parameters (*Table 2*). The ECP nurse explained that prior to the ECP treatment date of a patient, one of the ECP nurses would phone the tertiary unit in order to evaluate the patient's condition and make arrangements for blood product transfusion before ECP if blood parameters were low.

Patient information leaflets regarding ECP preparation and treatment side effects were given to the nurses on the ward to distribute to patients as required, as well as information on how to access the recently developed website containing an in-house video of the service.

Since its implementation, the outreach service has treated patients in a variety of medical environments, ranging from protective isolation bone marrow transplant units and protective isolation, to high dependency and intensive care units.

Six-month service review (July 2013 to January 2014)

Following a 6-month review of the outreach service, it was noted that there had been intermittent deferral of patient treatments for reasons that could have been avoided. It became apparent after further investigation that the underlying reasons

were that information had not been disseminated to other nurses on the ward and a basic lack of knowledge regarding patient criteria for treatment.

Examples of reasons for patient deferral were: the patient's blood parameters were too low, pyrexia (38°C or above), blood not ordered for a blood prime treatment, and the insertion of an intravenous device where the lumen size was too small to draw blood at the correct speed for the ECP machine.

Therefore the following recommendations were made by the ECP unit: the ECP nurse would telephone the tertiary ward the day before treatment and check progress and blood parameters of patient and request blood products if required.

The ECP unit then developed a treatment booklet for patients, which also contained the unit's website address and encouraged patients and staff to access it. This was in place of the patient leaflet previously used.

The telephone call the day before treatment had a positive result with far fewer treatment deferrals. The tertiary ward also developed a large treatment sticker for the ECP nurse to use and insert in the medical notes on completion of an ECP outreach treatment. The sticker was A5 in size containing medical documentation from the ECP nurse and specific details of the treatment given, such as:

- Patient observations and drug administration
- Space to insert notes on any issues during treatment
- The ECP nurse's signature to corroborate that specific requirements had been discussed
- Plans for the next treatment and handover to the patient's named nurse.

The ECP unit is now developing a treatment sheet to use in other outreach facilities. Treatment documentation by the ECP nurse also takes the form of an ECP care plan, which returns to the ECP unit with the nurse. It contains nurse and doctor assessments of the patient, patient self-evaluation and the 2-day ECP treatment plan.

ECP outreach service development at other hospitals

Following the original outreach project, another contract was secured to deliver ECP outreach treatment with training support to a paediatric inner city hospital over 80 miles away. Therefore, to accommodate two separate hospitals with ECP took careful planning with set days allocated for each hospital on the duty rota.

AGVHD carries a high mortality rate (Das-Gupta et al ,2014) and the accommodation of this patient is classed as a priority. So, to ease off-duty planning, the outreach ECP team developed an SOP to accommodate the patient with AGVHD that involves the rescheduling of less urgent cases under the guidance of the ECP consultant. This includes altering staffing and day-case ECP to accommodate the release of a nurse to the outreach hospital at short notice.

Overnight accommodation for the nurse travelling to the inner city paediatric unit was also included in the planning so that this patient could receive two consecutive days' treatment. *Table 3* summarises the caseload of the ECP outreach service. Following this initiative the paediatric hospital has commenced its own ECP service.

Table 3. Summary of ECP outreach activities (data collected 2013–2017)

Number of outreach hospitals: 2 Total number of patients: 28	Hospital 1: Adult hospital	19 adult patients treated (data collected 2013–2017) Total number of treatments delivered: 272
	Hospital 2: Paediatric hospital	9 paediatric patients treated (data collected November 2014–March 2016) Total number of treatments delivered: 260
Initial diagnosis / transplant type	Haematological (bone marrow/stem cell transplant): 25 Solid organ transplant: 3	
Mortality	17 died 11 have survived to date	
Gender	Male: 19 Female: 9	
Age range	4 months to 71 years (mean age 27 years)	
Types of transplant:	Donor lymphocyte infusion (DLI)*: 6 Matched unrelated donor (MUD): 10 Sibling matched: 6 Multivisceral: 1 Bowel: 1 Umbilical cord: 1 Unrecorded: 3	
Type of conditioning	Myeloablative: 4 Reduced: 12 Unrecorded: 12	
Site of AGVHD involvement (some had more than one site)	Skin: 22 Eyes: 1 Gut: 18 Liver: 10	

*Used on hematopoietic stem cell transplant patients with less than full chimerism

Conclusion

ECP is a more efficient therapy for AGVHD when used at early onset with an intensive schedule. It has a significant advantage in risk–benefit ratio, notably because of its efficacy and its immunomodulatory role without reported immunosuppression (Greinix et al, 2000; Knobler et al, 2014). However, the duration of response is not frequently reported.

It is suggested, therefore, that through the development of the fast-response ECP outreach service more patients with AGVHD will have a treatment that would have been previously denied. There have been anecdotal reports of improvement in quality of life since the development of this service and data are still being collected for audit purposes. The unit continues to develop its outreach service and has provided ECP to four other hospitals since 2017. **BJN**

Declaration of interest: AA has received speaker fees from Mallinckrodt Ltd

Alfred A, Taylor PC, Dignan F et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. Br J Haematol. 2017; 177(2):287–310. https://doi.org/10.1111/bjh.14537

KEY POINTS

- Extracorporeal photopheresis (ECP) is a second-line treatment for acute graft versus host disease, but is only available in a limited number of regional centres
- As outlined here, service evaluation and collaboration with tertiary centres enabled service improvement and enhanced patient care
- The development of an outreach service facilitated ECP treatment previously denied to this patient group
- The experience of this service shows that ECP outreach is a realistic alternative to providing an outpatient-only facility
- Because a new acute referral is classed as a priority, alteration of the day-case workload at short notice to release a nurse specialist is required

Bladon J, Taylor PC. Photopheresis up-regulates CD36 on monocytes and reduces CD25(+) and CD28(+) T cell numbers. Photodiagnosis Photodyn Ther. 2005; 2(2):119–127. https://doi.org/10.1016/S1572-1000(05)00034-7

Das-Gupta E, Greinix H, Jacobs R et al. Extracorporeal photopheresis as second-line treatment for acute graft-versus-host disease: impact on six-month freedom from treatment failure. Haematologica. 2014; 99(11):1746–1752. https://doi.org/10.3324/haematol.2014.108217.

Greinix H, Volc-Platzer B, Kalhs P et al. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. Blood. 2000; 96(7): 2426–2431. http://www.bloodjournal.org/content/96/7/2426

Hart JW, Shiue LH, Shpall EJ, Alousi AM. Extracorporeal photopheresis in the treatment of graft-versus-host disease: evidence and opinion. Therapeutic Advances in Haematology. 2013; 4(5): 320–334. https://doi.org/10.1177/2040620713490316

Howard J, Barnes K. Addressing workforce capacity and safety issues for new nurse-led services through competency modelling. Clinical Governance: an International Journal. 2012; 17(4): 317–331. https://doi.org/10.1108/14777271211273206

Jacobsohn D, Vogelsang B. Acute graft versus host disease. Orphanet Journal of Rare Diseases. 2007; 2:35. https://doi.org/10.1186/1750-1172-2-35

Jagasia MH, Greinix HT, Arora M et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015; 21(3):389–401.e1 (Epub December 2014) https://doi.org/10.1016/j.bbmt.2014.12.001

Knobler R, Berlin G, Calzavara-Pinton P et al. Guidelines on the use of extracorporeal photopheresis. J Eur Acad Dermatol Venereol. 2014; 28 (Suppl 1):1–37. https://doi.org/10.1111/jdv.12311

Macmillan Cancer Support. Graft-Versus-Host-Disease. 2014. http://tinyurl.com/ydgjpreh (accessed 9 April 2018)

Marsh S, Pittard A. Outreach: 'the past, present and future'. Continuing Education in Anaesthesia Critical Care & Pain. 2012; 12(2): 78–81. https://doi.org/10.1093/bjaceaccp/mkr062

Martin PJ, Rizzo JD, Wingard JR et al. First and second-line systemic treatment of acute graft versus-host disease: recommendations of the American Society of Blood and marrow Transplantation. Biol Blood Marrow Transplant. 2012; 18(8):1150–1163. https://doi.org/10.1016/j.bbmt.2012.04.005.

Van Lint MT, Milone G, Leotta S et al. Treatment of acute graft versus host disease with prednisolone: significant survival advantage for day +5 responders and no advantage for no responders receiving anti-thymocyte globulin. Blood. 2006; 107(10): 4177–4181. https://doi.org/10.1182/blood-2005-12-4851

CPD reflective questions

- Reflect on whether an outreach facility could be integrated into your own clinical setting to improve patient care. What governance issues would you have to consider?
- Could you develop a triage system to enhance day-case patient care? What would this need to consider?
- What patient information would you include in either a patient information booklet or a website design for your service to improve patient and professional access to information in your clinical area?