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Extracorporeal Photo-apheresis for the Treatment of Steroid-Resistant Graft Versus Host Disease

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Abstract

Acute and chronic graft versus host disease are frequent and potentially severe complications of allogeneic hematopoietic stem cell transplantation and are among the leading causes of non-relapse transplant-related mortality. For patients with steroid refractory disease, prognosis is particularly poor and although a variety of treatment options are available, responses are commonly transient and the side effects often intolerable. Since it was first introduced for the treatment of cutaneous T cell lymphoma, extracorporeal photo-apheresis has been utilized as an immunomodulatory therapy for certain autoimmune diseases and solid organ transplant rejection. Recently, extracorporeal photo-apheresis has become a promising alternative for patients with graft versus host disease with disabling or potentially lethal complications. Here we review the experience of extracorporeal photo-apheresis for the treatment of steroid refractory acute and chronic graft versus host disease based on the current literature.

Graft Versus Host Disease

Approximately 15-20,000 allogeneic hematopoietic stem cell transplants (HSCT) are performed each year worldwide for individuals with malignant and non-malignant diseases [1]. The number HSCTs has increased steadily over the past two decades due to improvements in outcome, expanded indications, and the ability to safely perform transplantation in older individuals [1]. Decreased transplant-related mortality has led to an increasing number of long-term survivors at risk of developing Graft-versus-host disease (GVHD). Along with infection, GVHD is the leading cause of non-relapse mortality following HSCT. Despite improvements in GVHD prevention, approximately 30 – 60% of matched sibling HSCT recipients will develop acute GVHD (aGVHD) and the rates are higher for unmatched or unrelated donors [2,3]. Acute GVHD is primarily T cell mediated, typically occurs early after transplant (within the first 100 days, although it can occur later) and preferentially effects the skin, liver and gastrointestinal (GI) tract. Severity of aGVHD is graded by the extent of involvement of these three target organs: grade I (mild), grade II (moderate), grade III (severe), and grade IV (very severe) [2,3]. Standard therapy for aGVHD is corticosteroids with or without a calcineurin inhibitor, to which 40 – 60% of patients will respond. For those with severe aGVHD or who

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are steroid refractory, the prognosis is quite grim. Five-year survival for grade III aGVHD is 25% and 5% for grade IV[2,3].

Chronic GVHD (cGVHD), an equally serious and potentially life threatening long-term complication of HSCT occurs in approximately half of HSCT recipients. cGVHD typically occurs after 100 days and can involve almost any organ of the body. It is a complex, multi-system disorder with alloimmune and autoimmune features. cGVHD is characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival. cGVHD can be manifested by clinical symptoms of almost any organ and is most frequently seen in the skin, eyes, mouth, GI tract, liver and lungs. cGVHD is often characterized by the development of one or more features of various autoimmune or immunologic disorders, such as scleroderma, Sjogren's syndrome, chronic immunodeficiency, and bronchiolitis obliterans [4]. cGVHD leads to impaired performance status, diminished quality of life and increased risk of mortality. Five-year survival rates for patients who develop cGVHD range from 40% for poor prognosis or "high-risk" cGVHD to 70% for "standard-risk" cGVHD. The incidence of cGVHD is increased in certain populations, especially recipients of peripheral blood or unrelated donor HSCT where it may be as high as 80%[5,6].

Standard front-line therapy for both acute and chronic GVHD typically consists of high-dose systemic corticosteroids. As noted above, approximately 40-60% of patients with acute and up to 70% of patients with chronic GVHD will respond to front line therapy. However, many patients need second-line therapies and for those who do respond treatment-limiting side effects often occur. The list of immunosuppressive drugs and other agents attempted for salvage therapy of acute and chronic GVHD is long and there is no standard approach to treatment of refractory GVHD. In cGVHD, the average response rate to salvage agents is approximately 35% and commonly these responses are only partial and short-lived, with high failure and complication rates. Thus, new treatment approaches are eagerly being sought [6,7].

Extracorporeal Photopheresis (ECP)

ECP is a therapeutic procedure originally brought into clinical medicine for the treatment of cutaneous T-cell lymphoma (CTCL)[8]. The procedure involves separating the white blood cells (buffy coat) from the plasma and red blood cells which are returned to the patient. The buffy coat leukocytes are then exposed to UVA irradiation following pretreatment with 8-methoxypsoralen, which results in apoptosis of the majority of cells within 48 hours [9]. The treated white blood cells are subsequently re-infused into the patient. *In vitro* and *in vivo* studies suggest that these treated white blood cells have significant immunomodulatory effects. The U.S. Food and Drug Administration has approved ECP for the treatment of cutaneous T-cell lymphoma. Over the past two decades, ECP has been further applied and studied in the treatment of several autoimmune diseases and GVHD. It has also been successfully used as a treatment for cardiac, renal and lung allograft rejection[10-14].

ECP treatment involves the infusion of large numbers of apoptotic cells and it has been clearly demonstrated in a number of model systems that the clearance of apoptotic cells can result in immunomodulation [15,16]. However, the specific mechanisms by which ECP works are poorly understood[17,18]. One proposed mechanism involves a shift in the balance of the Type 1 (Th1) and Type 2 (Th2) CD4+ T cell profile. Gorgun et al demonstrated that patients with cGVHD treated with ECP demonstrated an increase in DC2 dendritic cell subsets and concomitant shift in Th2 cytokine production by T cells [19]. However, in CTCL where early stage disease is associated with Th2 skewing, ECP results in a shift toward Th1 cytokines and a restoration of the normal Th1/Th2 balance. In addition, Silva et al demonstrated an increase in Th1 cells in patients with cGVHD[20]. Rather than discounting a role for cytokine modulation with ECP, these discrepancies likely reflect the complexity of the Th1/Th2 system

and the biologic effects of ECP. In fact, additional reports have shown that ECP alters cytokine profiles with increases in IL-10, a cytokine frequently associated with immunosuppression [21,22]. One important issue to consider when interpreting these studies is that many of the diseases treated with ECP, including GVHD, are associated with a Th1/Th2 shift such that it is difficult to ascertain whether the restoration of this balance reflects a therapeutic mechanism or is simply a marker of disease improvement. Another area that has been explored as a potential mechanism of ECP in the treatment of GVHD is the impact of ECP on dendritic cells. Patients treated with ECP have been shown to demonstrate decreases in circulating CD80+ and CD123+ dendritic cell subsets [19,23]. Recent studies have also revealed that ECP also causes a shift toward immature dendritic cell populations with low level co-stimulatory molecule expression and decreased migratory response to MIP-3 β , decreased T cell proliferation and increased production of IL-10, which blocks dendritic cell maturation and diminishes allostimulatory capacity[24-26]. Importantly, these changes characterize tolerogenic dendritic cells[27-29]. Malech and colleagues at the NIH demonstrated that there is an increase in central memory CD8 T cells and a decrease in central memory CD4 T cells in patients with cGVHD. They further showed that the balance of memory T cells normalizes after ECP treatment in tandem with improvement of clinical symptoms[30]. Finally, the expansion of regulatory T cells has been associated with ECP treatment in humans[26,31,32] and in murine models[33,34]. Although the clinical use of ECP has preceded a clear understanding of the mechanism by which this therapy exerts its therapeutic effect, emerging data from clinical studies, animal models and in vitro studies are beginning to shed light on the immune modulation that occurs. In addition, rapid advancements in related fields such as apoptotic cell clearance, regulatory T cell biology and tolerogenic dendritic cells are further guiding investigations into ECP mechanism.

ECP for GVHD

Over the past decade and a half, there has been an emerging literature exploring the utility of extracorporeal photopheresis (ECP) in the treatment of GVHD[20,35-62]. Small pilot and early phase trials suggest that ECP is an effective treatment for both acute and chronic GVHD. In 2000, Greinix et al reviewed the experience of ECP for severe acute and chronic GVHD [63]. The authors summarized the results of 11 previously published studies involving 151 patients. As most studies were rather small and treatment criteria differed, the response rates in aGVHD were highly variable, with responses seen primarily in skin and liver manifestations. Responses were more consistently seen in steroid refractory cGVHD with reported response rates of 40 - 100% and improvements noted in all organs. Importantly, adverse reactions to ECP were uncommon and typically consisted of nausea, hypotension, dizziness, and cytopenias. These side effects were reported as mild in all cases and of significance, the authors did not report an increase in reported infections [63].

ECP for Acute GVHD

Table 1 summarizes the largest published series of ECP for aGVHD. In general, aGVHD patients with low stage involvement are more likely to respond to therapy in comparison to higher-grade disease. Initial publications consist of case reports and small series with outcomes that varied from responses seen in 3 of 4 patients[62], to 0 of 6 patients with grade IV hepatic aGVHD[57]. The first sizable report of ECP in the setting of aGVHD was published by Greinix et al. in 2000 [64]. The authors presented 21 patients with steroid-refractory grade II - IV aGVHD. After three months of ECP, 60% of patients achieved a complete resolution of GVHD manifestations. Patients with lower grade aGVHD fared better than those with higher-grade disease, with a complete response (CR) rate of 100% for grade II, 67% for grade III, and 12% for grade IV. When evaluating organ specific responses, CRs were achieved in 60% of patients with cutaneous, 67% with liver, and none with GI involvement. Patients who manifested CRs

to ECP had higher 4-year survival rates than those who did not[64]. The authors went on to perform an extended phase II study of 59 patients (including the 21 patients published previously) with steroid-refractory aGVHD (grades II to IV). These patients were initially treated with 2 consecutive cycles every 1-2 weeks until improvement, then 2 consecutive cycles every 2-4 weeks. Complete resolution of GVHD was achieved in 82% of patients with cutaneous involvement, 61% with liver involvement, and 61% with GI involvement, the latter in contrast to the absence of GI responses in their initial report. Complete response rates by grade were 86%, 55%, and 30% for grades II, III, and IV respectively. Not unexpectedly, those with CRs to ECP had a higher probability of survival (59%) in comparison to those without (11%). The authors concluded that intensified ECP is highly effective in the treatment of aGVHD and that sustained responses are associated with over 50% long-term survival[41]. The authors did not comment on adverse events or infectious complications experienced by patients on this study.

Some of the larger ECP studies in the setting aGVHD included pediatric patients. The first is a report by Messina et al. who studied 77 pediatric patients with refractory acute (n = 33) or chronic (N = 44) GVHD in four Italian pediatric hospitals. The 33 patients with aGVHD were treated with ECP at a median time of 45 days following HSCT for a median time of 74 days (median 8 cycles). Eighteen of the 33 (54%) had a CR (2 grade I, 6 grade II, 8 grade III and 2 grade IV). An additional 7 patients (24%) had partial responses. Maximal responses were seen after 8 weeks of treatment. GVHD involving skin, liver and GI tract responded completely in 76%, 60% and 75% of patients respectively. The 5-year overall survival was 69% for responding patients versus 12% for non-responders [50].

A second pediatric study evaluated the use of ECP for aGVHD following umbilical cord blood transplantation. Sixteen of 31 patients with grade II–IV aGVHD responded well to steroids and 15 did not and therefore went on to receive ECP therapy. All patients started ECP within 100 days of HSCT. Eligibility criteria for starting ECP included steroid resistance, steroid dependence or viral reactivations (e.g., CMV, EBV). ECP therapy consisted of 2 consecutive sessions weekly for 1 month, then 2 consecutive sessions every 2 weeks for 2 months, followed by 2 consecutive sessions monthly for a minimum of 3 months. Response to treatment was categorized as follows: resolution of all signs was considered a complete response (CR); at least a 50% improvement was classified as a partial response (PR); and stable or progressive disease was categorized as no response (NR). The CR rate was 73% for those treated with ECP, whereas a CR rate of 56% was seen in the 16 patients who initially responded to steroids and therefore did not receive ECP. The 2-year overall survival and progression-free survival rates were 85 and 87% in the ECP group versus 57 and 67% in the steroid responsive group. Four of 15 patients in the ECP group experienced septic episodes and one case of aspergillus was reported. The authors concluded that patients treated with ECP following umbilical cord blood transplantation had improved outcomes in comparison to those treated with corticosteroid therapy[37].

Berger and colleagues retrospectively evaluated pediatric patients with steroid resistant GVHD including 15 patients with aGVHD and 10 with cGVHD. aGVHD was staged as II (n=7), III (n=4), and IV (n=4) and the median interval from the onset of aGVHD and start of ECP was 25 days. ECP treatment was administered as 2 consecutive sessions weekly for 1 month, then 2 consecutive sessions per week every other week for 2 months, then 2 consecutive sessions monthly for 3 months. The response rate was 100% for grade II, 75% for grade III, and 0% for grade IV. In multivariate analysis, the strongest predictor for ECP response was aGVHD severity. ECP non-responders had a higher risk of transplant-related mortality[38].

A recent retrospective study analyzed 23 adults with steroid-refractory grade II (n=10), III (n=7) or IV (n=6) aGVHD. Patients received 2 consecutive sessions weekly for 1 month, then

2 consecutive sessions every 2 weeks for 2 months, followed by 2 consecutive sessions monthly until resolution or stabilization of symptoms. The median duration of ECP therapy was 7 months (1–33). Patients were graded according to the Glucksberg-Seattle scale for aGVHD and were evaluated monthly for response. Twelve patients (52%) had CRs in all organs. Twelve patients (52%) on the study died, 10 of GVHD with or without infections and two died of disease relapse. Overall, the average grade of aGVHD was reduced, as was the average dose of methylprednisolone. Complete responses were obtained in 70% of patients with grade II, 42% with grade III, and similar to other studies, no responses were seen in patients with grade IV aGVHD. When evaluating individual organ systems, CRs were most frequently seen in the skin (66%), followed by the GI tract 40%, and less so in the liver (27%). A trend for improved survival was also seen in grade III–IV aGVHD treated with ECP as compared to matched controls (38 vs. 16%). The investigators found patients treated earlier, within 35 days from onset of aGVHD, had higher responses than those started later after onset. In general, treatments were well tolerated, with a few patients experiencing low-grade fevers, weakness and hypotension within 12 hours of ECP. Several patients also required red blood cell (n = 9) or platelet transfusion (n = 7) support. The authors conclude that ECP is a promising treatment option for patients with steroid refractory aGVHD and should be considered early in the course of disease [36].

ECP for Chronic GVHD

Many of the initial reports of ECP for patients with cGVHD were poorly designed with unclear endpoints. However, more recent studies report response rates of up to 61 - 71% particularly of skin, liver, eye and oral manifestations including individuals with steroid refractory cGVHD [44-46][48]. Regimen-related details such as the optimal duration and approaches to end therapy (i.e., taper vs. abrupt cessation) have not been rigorously investigated. The largest published series of ECP for cGVHD are summarized in Table 2.

In 2006, Couriel et al. published a retrospective analysis of 71 patients with severe cGVHD treated with ECP. Therapy included 2 – 4 treatment sessions per week until a PR was observed. Therapy was subsequently tapered by 1 session per week and eventually patients were placed on a maintenance regimen of 2 treatments every 2 weeks. Overall response rate (CR + PR) was 61% (n = 43) and 20% (n = 14) had CRs. The highest rates of responses were seen in skin, liver, oral mucosa, and eye. Thirty-three (59%) patients with skin disease responded, including 14 of 21 (67%) who presented with sclerotic skin changes. Median time to response after ECP initiation was 46 days. Thrombocytopenia was associated with a lower response rate and there was a trend toward a higher response rate in patients with de novo cGVHD in a subset of less heavily pretreated patients. A sustained response was seen in 27 (69%) of 39 patients alive at 6 months. In addition, many patients were able to decrease or discontinue steroid therapy and the cumulative incidence of steroid discontinuation at 1 year was 22%. Overall survival after initiation of therapy was 53% at 1 year. Toxicity occurred in 4 patients and included mild abdominal pain (n=1), hypotension (n=1), hypertension (n=1), and fever (n=1). Several patients required red cell and platelet transfusion support. Forty-two patients died with a median follow up of 34 months. The leading cause of death was cGVHD with infection. The strongest predictors of non-relapse mortality were response to ECP and low platelet count ($< 100,000/\text{mm}^3$) at initiation of therapy [45].

Foss, et al. described a prospective evaluation of 25 predominantly adult patients with extensive, steroid-refractory skin and visceral cGVHD. The ECP schedule was administered as 2 consecutive days every 2 weeks in 17 patients and once a week in eight patients until best response or stable disease was achieved. All patients had skin involvement and additional organ manifestations varied. All patients failed standard therapy with steroid, calcineurin inhibitor and/or mycophenolate mofetil and had a minimum weight of 40 kg. The median time of the

initiation of ECP from transplant was greater than two years with a median duration of therapy of 9 months. Patients were evaluated monthly for response. Skin response was considered a 50% or greater body surface area decrease in rash, or decreases in skin thickness or range-of-motion around a joint. Improvement in liver involvement was considered with a 50% or greater improvement in bilirubin (or >25% for baseline bilirubin > 8mg/dL). Gastrointestinal response required improvement in both decreased stool output and improvement on rectal biopsy. The overall response rate of at least one organ was 64%. Twenty patients (80%) had improvement in cutaneous GVHD, including 6 patients that experienced softening of sclerotic skin and healing of cutaneous ulcers in 3 patients. Six patients (46%) had healing of oral ulcerations. There were also reports of improvement of GI, eye and pulmonary symptoms, although the numbers for these were small. Although not considered a response by study criteria, steroid sparing or discontinuation of immunosuppressive medications was achieved in 80% of patients. ECP schedule did not appear to effect response rates, nor did duration from transplant to ECP initiation. In contrast to the Couriel study, progressive onset cGVHD had a trend towards higher response rates than those with de novo onset. Fifteen patients (60%) had adverse events, the majority of which were infectious complications. One patient with underlying GI GVHD and CMV colitis experienced a GI bleed. The authors concluded that ECP was generally well tolerated and effective in the management of cGVHD. In particular, the authors noted that ECP provided a steroid sparing alternative therapy [46].

In order to determine clinical factors associated with response to ECP, Rubegni et al evaluated 32 patients with refractory cGVHD. A total of 1128 cycles of ECP were delivered. ECP was deemed ineffective when progression was observed in one of the organs involved, when it was necessary to increase the dose of immunosuppressants, or when CR was not observed in any organ and immunosuppressants were not reduced by more than 50%. A positive response was defined as either “determinant” when CR was observed in all organs after the start of ECP and when the dose of immunosuppressants could be reduced by at least 50% with respect to initial therapy, or “good” in all other cases. The authors report a positive outcome in 25 patients (78%). Best responses were seen in skin, oral mucosal, liver and conjunctival manifestations. They reported high response rates (90%) in patients with thrombocytopenia (platelet count < 100,000/ μ L). However, they did not identify any statistically significant factors associated with response, with the exception of the number of immunosuppressive agents at the time of initiation of ECP therapy and the time interval between transplant and the start of ECP. Only minor side-effects were reported (hypotension, hematomas at antecubital venipuncture sites), none of which required interruption of treatment [48].

The most recent and one of the largest studies for cGVHD evaluated the safety and efficacy of 3 - 6 months of ECP combined with standard therapy vs. standard therapy alone. All patients had steroid refractory cutaneous manifestations of cGVHD. Ninety-five patients were randomized to either ECP and standard therapy (n = 48) or standard therapy alone (n = 47). Efficacy was measured by a skin score assessment at the 3-month time point. ECP was administered as 3 times weekly during the first week, on 2 consecutive days weekly until 3 month, and for responders continued on a schedule of 2 treatments monthly. A greater proportion of patients in the ECP arm versus the control arm had both a reduction in steroid dose and a decrease in their skin score (8.3% vs 0%), which was statistically significant (P= 0.4). In addition, they found a statistical improvement in eye and oral cGVHD in the ECP treated group as well. Overall, ECP appeared to be well tolerated. Adverse events occurred evenly in both groups, with infection and nausea the most commonly reported. The one exception was that anemia was more frequently documented in the ECP group. The authors suggest that this study supports that ECP may be effective in treating cGVHD of the skin and may have a steroid sparing effect in the overall treatment of cGVHD [35].

The treatment of children in ECP trials for cGVHD is more sporadic than in aGVHD and many trials restrict enrollment for individuals weighing < 30 – 40 kg due to the large volume of extracorporeal blood required. However, in the study by Messina (partly described in the previous section), which evaluated the use of ECP in 77 pediatric patients with acute and chronic GVHD, children weighing as little as 10 kg were eligible to enroll. The investigators used lower volumes of serum and buffy coat and/or higher hemoglobin requirements than in adults and were able deliver therapy with minimal side effects. Hypotension was seen in nearly 50% of patients, but was mild and did not require discontinuation of treatment. An overall response rate of 59% was reported for children with cGVHD, 44% were able to discontinue all immunosuppressive medications, and 29% were able to reduce immunosuppression. Overall survival was increased in those patients who responded to ECP [50]. One of 77 patients (acute and chronic) developed gastrointestinal bleeding, a previously reported complication of ECP [46,50,65]. Another recently published pilot study from Italy enrolled 25 pediatric patients with acute and chronic GVHD. All patients < 40kg were treated on a continuous flow device, including two patients between 20 - 30 kg. All patients tolerated the procedure well and there were no reported occurrences of hypotension. The most commonly observed side effect was abdominal pain during the procedure (20%). Transient decreases in platelet and white blood cell counts were reported in 80% of patients. No infections or grade III or IV toxicities were noted. Responses occurred in half of the patients. All patients with limited cGVHD had complete responses [38].

Toxicity of ECP

The majority of published ECP trials report minimal side effects, consisting primarily of mild hypotension (5-50% of patients), abdominal pain, and hematomas at the site of vascular access during apheresis. Also, rarely reported are cases of gastrointestinal bleeding [46,50,65] and adverse effects related to the need for central venous access device, which includes catheter-related infections and line-associated blood clots. Other noted toxicities include mild cytopenias that are typically easily managed with iron supplementation, erythropoietin treatment, and/or transfusions. The amount of immunosuppression occurring secondary to ECP is unclear. Infections are reported in patients receiving ECP and include CMV reactivation, line infections, and pneumonias. As this group of patients is at very high risk for infection due to underlying disease and concomitant immunosuppression, it is not known if this is potentiated by ECP [44-46,48,65].

Conclusion

ECP has been established as effective in the treatment of GVHD. It has shown particular promise in the skin manifestations of aGVHD and to be a steroid sparing modality for cGVHD. Also, it is one of the few treatments to have recurrently shown activity in drug-resistant fibrotic manifestations of cGVHD, such as sclerotic skin involvement. Although the mechanisms of efficacy are poorly understood and the optimal therapeutic regimens, including the schedule, duration, and approach to weaning and discontinuation, have not been well delineated, ECP offers hope for this devastating and treatment-resistant complication of HSCT. ECP warrants further evaluation and development in order to define the optimal therapeutic approach and the most appropriate patient population.

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Table 1
Acute GVHD Series

Number of Patients	Grade/organs	ECP Schedule	Responses	Author
23	II-IV Steroid Refractory	2 consecutive sessions per week for 1 month, then 2 consecutive sessions per week every other week $\times$ 2 months, then 2 consecutive sessions monthly	CR 52% Grade II (70%) Grade III (42%) Grade I (0%) Skin CR 66% Liver CR 27% GI CR 40%	Perfetti 200836
15 (pediatric)	II-IV Steroid Refractory or Viral Reactivation	2 consecutive sessions per week for 1 month, then 2 consecutive sessions per week every other week $\times$ 2 months, then 2 consecutive sessions monthly $\times$ 3 months	CR 73% PR 27% Grade II (100%) Grade III (34%) Grade IV (60%)	Calore 200837
15 (pediatric)	II-IV Steroid Refractory	2 consecutive sessions per week for 1 month, then 2 consecutive sessions per week every other week $\times$ 2 months, then 2 consecutive sessions monthly $\times$ 3 months	GVHD-free OS 62% Grade II (100%) Grade III (75%) Grade IV (0%)	Berger 200738 (Massimo)
59	II-IV Steroid Refractory	2 consecutive sessions per 1-2 weeks until improvement, then 2 consecutive sessions per 2-4 weeks to maximal response	Skin CR 82% Liver CR 61% GI CR 61% Grade II (86%) Grade III (55%) Grade IV (30%)	Greinix 200641
12	I-IV Steroid Refractory	Initially 2 $\times$ weekly for 3 weeks, then weaned	ORR 75%	Garban 200547
33 (pediatric)	I – IV Steroid Refractory	2 consecutive sessions weekly for 1 month, then 2 consecutive sessions every 2 weeks for 2 months, then 2 consecutive sessions monthly	CR 54% PR 21% Skin CR 76% Liver CR 60% GI CR 7.5%	Messina 200350
9 (pediatric)	II-IV Steroid Refractory	3 $\times$ weekly until improvement, then 2 consecutive sessions every 2 weeks for 3 months, then taper	ORR 78%	Salveneschi 200152

RR = response rate; CR = complete response; PR = partial response; SD = stable disease; ORR = overall response rate; GI = gastrointestinal; OS overall survival.

Table 2
Chronic GVHD Series

Number of Patients	Grade/organs	ECP Schedule	Responses	Author
48 of 95 randomized	Steroid Refractory with skin involvement	3 session $\times$ 1 week, 2 sessions weekly weeks 2 – 12, then 2 session monthly weeks 12 -24	Skin ORR 40% Eye 30% Oral 53%	Flowers 200835
10 (pediatric)	Steroid Refractory	2 consecutive sessions weekly $\times$ 1 month, then 2 consecutive sessions per week every other week $\times$ 2 months, then 2 consecutive sessions monthly $\times$ 3 months	Limited ORR 100% Extensive ORR 28%	Berger 200738 (Massimo)
14	Extensive Steroid Refractory	Initially 3 $\times$ weekly, then weaned when PR observed	Skin CR 21% Skin PR 29% Skin SD 50%	Bisaccia 200643
71	Steroid refractory	2 -4 sessions per week until response, then weaned	ORR 61% CR 20%	Couriel 200645
25	Extensive Steroid refractory	2 consecutive sessions per week every other (17) or once weekly (8) until best response	ORR 71%	Foss 200546
32	Steroid refractory	Not available	ORR 78%	Rubegni 200548
15	Steroid refractory	Initially 2 $\times$ weekly for 3 weeks, then weaned	CR 73% PR 18%	Garban 200547
8	Extensive Steroid Refractory	2 consecutive sessions every 2-4 weeks until resolution	ORR 75%	Ilhan 200449
44	Steroid Refractory	2 consecutive sessions weekly for 1 month, then 2 consecutive sessions every 2 weeks for 2 months, then 2 consecutive sessions monthly	CR 44% PR 29%	Messina 200350
32	Steroid Refractory cutaneous	Not standardized	CR 22% PR 34% Steroid sparing 64%	Apisarnthanarax 200356
14 (pediatric)	Steroid Refractory	2 consecutive sessions every 2 weeks $\times$ 3, then 2 consecutive sessions every 3, then taper	CR 29% PR 36%	Salvaneschi 200152
11	Steroid Refractory	2 consecutive sessions every 1-2 weeks, then weaned	Skin CR 64%, 1 Skin PR 9% Skin SD 18% Oral No responses	Zic 199953
11	Extensive Cutaneous	2 sessions monthly $\times$ 4, then 1 session monthly $\times$ 3	ORR 82%	Child 199954
18	Steroid Refractory	Unknown	ORR de novo 50% ORR progressive 25%	Smith 199857
9		2 consecutive sessions weekly, then 2 consecutive sessions monthly $\times$ 3 months	ORR 67%	Dall'Amico 199862
15	Extensive	2 sessions every 2 weeks	Skin CR 80%	Greinix 199861

RR = response rate; CR = complete response; PR = partial response; SD = stable disease; ORR = overall response rate;

* see text for study details.