

Real-world clinical characterization, healthcare resource utilization and productivity loss in chronic graft versus host patients exposed to extracorporeal photopheresis in Sweden

Frida Schain^a, Constance Boissin^b, Tamas Laczik^c, Stefano Fedeli^c, Mats Remberger^d, Ola Blennow^e, Josefina Dykes^f, Torsten Eich^g, Christina Jones^a, Jonas Mattsson^{h,i,j}, Gösta Berlin^{k,*}

^a Schain Research, Bromma, Sweden

^b Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden

^c KTH-Royal Institute of Technology, Stockholm, Sweden

^d KFUE, Uppsala University Hospital and Institution of Medical Science, Uppsala University, Uppsala, Sweden

^e Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

^f Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Lund, Sweden

^g Uppsala University, Institution for Immunology, Genetics and Pathology, Uppsala, Sweden

^h Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada

ⁱ Gloria and Seymour Epstein Chair in Cell Therapy and Transplantation, Canada

^j Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

^k Department of Clinical Immunology and Transfusion Medicine, and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

ARTICLE INFO

Keywords:

Extracorporeal photopheresis
Healthcare resource utilization
Hematopoietic stem cell transplantation
Population-based registry
Chronic graft versus host disease

ABSTRACT

Background: Extracorporeal photopheresis (ECP) is frequently used to treat moderate-severe chronic graft versus host disease (cGVHD), however limited data exists describing ECP treatment effects on healthcare and societal costs. We aimed to characterize clinical and health economic outcomes and productivity loss in cGVHD patients exposed to ECP.

Methods: We identified 2708 patients aged ≥ 18 years with a record of allogeneic hematopoietic stem cell transplantation (HSCT) in the Swedish Patient Register between 2006 and 2020. Patients exposed to ECP from 3-months post HSCT (index) were included ($n = 183$). Data was linked to the Prescribed Drug Register, the Cause of Death Register, and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA). **Results:** The median patient age at index was 51 years (IQR1–3; 38–61). In the 3-month period before ECP initiation compared to 9–12 months post-ECP, the cumulative three-month dose per patient decreased prednisolone/prednisone (1,381 mg vs. 658 mg, $p < 0.001$) and cyclosporin (12,242 mg vs. 3,501 mg, $p < 0.001$). Infection incidence also decreased over the same period (79.2% vs 59.1%, $p < 0.001$). Time spent in healthcare decreased from 68.9% to 22.1% from the first and fifth follow-up year respectively, and corresponding annual healthcare cost reduced from €27,719 to €1,981. Among patients < 66 years of age, sickness-related workplace absence decreased from 73.2% to 31.9% between the first and fifth follow-up year, with median annual productivity loss decreasing from €20,358 to €7,211 per patient.

Conclusions: ECP was associated with reduced use of corticosteroids, immunosuppressive agents, and fewer infections. Furthermore, cost and healthcare utilization decreased over time.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a

treatment intervention with curative potential for several benign and malignant conditions. However, approximately 30–70% of HSCT recipients who survive at least 100 days following HSCT develop chronic

* Correspondence to: Department of Clinical Immunology and Transfusion Medicine, Department of Biomedical and Clinical Sciences Linköping University, Linköping 581 85, Sweden.

E-mail address: gosta.berlin@regionostergotland.se (G. Berlin).

<https://doi.org/10.1016/j.transci.2023.103705>

Received 24 August 2022; Received in revised form 9 March 2023; Accepted 19 March 2023

Available online 21 March 2023

1473-0502/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

graft-versus-host disease (cGVHD) [1]; a debilitating and life-threatening inflammatory complication associated with heterogeneous organ damage [1–3]. cGVHD has high mortality rates [4] and is the leading cause of non-relapse mortality from two years post HSCT [5,6]. High dose corticosteroids and immunosuppressive agents are typically used as frontline treatment [7–11], however on average half of all patients will become refractory to treatment [12]. Long-term treatment with high-dose corticosteroids is also associated with significant toxicity and a high proportion of cGVHD patients develop treatment-related comorbidities including type 2 diabetes, osteoporosis, and hypertension [13]. Furthermore, immunosuppression is associated with higher risk of infection and is a major cause of death in cGVHD patients [1]. The costs associated with cGVHD management are significant; with cumulative three-year healthcare resource utilization (HRU) cost for mild and moderate-severe cGVHD patients in Sweden estimated at over €70,000 and €100,000, respectively [14].

ECP is a leukapheresis-based therapy where patients' leukocytes are collected, treated ex vivo with methoxsalen and exposed to ultraviolet light, and returned to the patient. ECP is widely recommended as second-line treatment for cGVHD [7,15–21]. While the immunomodulatory mechanism of action is not fully elucidated, ECP has been shown to be effective in treating cGVHD while being safe and associated with minimal side effects [21–23]. Prospective and retrospective studies focused on real-world effectiveness of ECP in cGVHD have mostly been small, single-site or regional studies [21], but none have shown a nationwide perspective. Furthermore, few have assessed long-term clinical outcomes, as well health economic factors associated with ECP treatment such as healthcare resource utilization [24] and productivity loss associated with workplace sickness absence [25].

The objective of the current study was to utilize patient data from linked, longitudinal population-based registers over a 15-year period to characterize burden of disease and the clinical and health economic outcomes associated ECP with treatment for cGVHD patients in clinical practice.

2. Material and methods

2.1. Ethics and linkage

This study was approved by the Swedish Ethical Review Authority (Dnr 2020–03027) and used nationwide Swedish registers held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden (SCB). Informed consent from patients was not required for secondary use of pseudonymised register data. Unique personal identification numbers allowed patient data linkage across the Patient Register, the Prescribed Drug Register, the Cause of Death Register, the Cancer Register and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA). To account for underreporting of ECP treatment records in the Patient Register, data enrichment was performed by accessing regional hospital payment systems. This additional data was available for all regions in Sweden except for Karolinska University Hospital.

2.2. Study population

Patients aged ≥ 18 years with a record of allogeneic HSCT in the Swedish Patient Register between January 2006 and July 2020 were identified (Supplementary Fig. 1). Within this population, patients with a record of ECP treatment from at least 3 months after HSCT (index) and onwards were included. End of follow-up was December 2020. Patients were excluded when ECP treatment was recorded within the first 3 months post HSCT only, or if death or emigration was less than 3 months post HSCT.

2.3. Statistical analysis

Univariate all-cause survival for HSCT patients exposed to ECP from 91 days post HSCT (index date) was calculated with Kaplan Meier analysis with 95% confidence interval (CI). Patients were followed until death or censoring due to end of follow-up. Survival analysis was performed using the R survival package.

To determine treatment pattern characterization, the proportion of HSCT patients who received ECP at each follow-up year post index date and the median number of treatments per patient per follow-up year were assessed. The number of treatments were defined as each date an ECP record was registered. Immunosuppressive drug use was based on ATC records registered pre- and post-ECP initiation. Cumulative drug dose per patient (mg) three months prior to ECP until one year after ECP (–3 to 0 m; 0–3 m, 3–6 m, 6–9 m, 9–12 m) were calculated. Statistical significance between the reference period (ref; –3 to 0 m prior to first ECP record) and time periods after treatment initiation were assessed by paired t-test.

Infection incidence was assessed pre- and post-ECP initiation (–3 to 0 m; 0–3 m, 3–6 m, 6–9 m, 9–12 m; see Supplementary Methods for infection definition codes). Statistical significance between the reference period (ref; –3 to 0 m prior to first ECP record) and time periods after treatment initiation were assessed by equality of proportion test. Stata SE v15 was used for analyses in for both treatment pattern characterization and infection incidence.

2.4. Healthcare resource utilization (HRU) and cost

The number of patients who accessed specialized healthcare (inpatient admissions and outpatient visits) were stratified per follow-up year. Average time spent in care per follow-up year was defined as the number of days in care for a given follow-up year/total person time contributed by patients for given follow-up year. Date of admission/discharge defined inpatient time in care, while each outpatient record was counted as one day. Direct medical cost was derived from Diagnosis Related Group (DRG) codes recorded in the Patient Register. HRU cost analyses follow-up was restricted to December 2019 due to lag time of the published annual weighted code costs (Socialstyrelsen). All costs were adjusted for inflation as of 2020 according to Swedish Consumer Price Index (Statistics Sweden). Cost was converted from Swedish Kronor to Euros based on the average conversion rate for 2020 according to the European Central Bank (1 Euro =10.4848 SEK).

2.5. Sickness absence and productivity loss

The proportion of time patients were absent from work was assessed for patients < 66 yrs of age (assumed retirement age in Sweden). Sickness absence days were defined as the cumulative number of days a patient received sickness benefit, preventive sickness benefit, occupational injury sickness benefit and/or rehabilitation benefit per year recorded in the LISA register (plus 14 days per follow up year to account for initial employer funding of sick leave). Productivity loss was defined based on an individuals' sickness absence days and their salary; calculated using earned income and work-related remuneration from the LISA register. LISA data was available for follow-up until December 2018. Productivity loss cost was multiplied by 1.3142 to account for payroll and social fees and converted to Euro as described above.

3. Results

3.1. Patient characteristics

2,708 patients with a record of allogeneic HSCT were identified in the Patient Registry (Supplementary Fig. 1). Patients were excluded who were exposed to ECP less than 3 months after HSCT only (n= 18), had an index date prior to 01.01.2006 (n= 12), and were under 18 years of age

at index (n= 14). Overall, 183 patients treated with ECP \geq 91 days post HSCT were included in the study population (Table 1). The median age at index was 51 years, with men representing 65.6% of all patients. The main underlying conditions were acute leukemia (43.2%) and chronic leukemia (15.3%). For HSCT, 16.9% of patients received stem cells from an unrelated donor, and 83.1% received peripheral blood stem cells (Table 1). The median follow-up time was 2.7 years.

3.2. ECP treatment pattern

The median time from index date to first ECP exposure was 7.8 months (IQR 1–3; 3–19). Median number of ECP treatments was 18 (IQR 1–3; 4–39) and mean was 17.8 (SD 42.6) (Table 2). Median time from index to first ECP for patients transplanted 2006–2015 was 10.1 months (IQR 2.7–26.8) compared to 7.1 months for patients transplanted in 2016–2020 (IQR 3.6–15.9), despite no significant difference in baseline characteristics (Supplementary Table 2). 112 of 183 ECP-treated patients (61%) received ECP within the first follow-up year from index date (Table 2). In the fifth follow-up year, 22 of 67 ECP-treated patients (32%) received treatment that year. During the 3-month period prior to first ECP treatment, 90.0% of patients (n= 165) received cyclosporine, 52.5% (n= 96) received prednisolone/prednisone, 9.8% (n= 18) received tacrolimus and 3.8% (n= 7) received ruxolitinib (Table 3).

3.3. Overall Survival, Corticosteroid and Immunosuppressant Usage, and Infections

The median overall survival time from index date was 6.0 years among all HSCT patients exposed to ECP treatment (Fig. 1). After ECP treatment initiation, patient use of prednisolone/prednisone and cyclosporin was reduced, when compared to the 3-month period prior to the first ECP treatment (Table 4). Cumulative dose dispensed by pharmacies per patient decreased for prednisolone/prednisone (1,381 mg versus 658 mg [9–12 months post ECP initiation], $p < 0.001$) and cyclosporin (12,242 mg versus 3,501 mg [9–12 months post ECP initiation], $p < 0.001$). Too few patients were treated with tacrolimus (n=

Table 1
Baseline characteristics for HSCT patients exposed to ECP.

Total, n (%)	183
Sex, n (%)	
Male	120 (65.6)
Female	63 (34.4)
Age, years	
Median (IQR 1–3)	51 (38–61)
Mean (SD)	48.9 (14.2)
Age group, n (%)	
18–39	55 (30.1)
40–59	76 (41.5)
\geq 60	52 (28.4)
Indication for HSCT, n (%)	
Hematological malignancy	
Acute leukemia	79 (43.2)
Chronic leukemia	28 (15.3)
Lymphoma	14 (7.7)
Myelodysplastic syndrome	22 (12.0)
Other hematological malignancy	10 (5.5)
Solid tumor	0 (0.0)
Other	30 (16.4)
Donor, n (%)	
Related	70 (38.3)
Unrelated	108 (59.0)
Unknown	5 (2.7)
Source of HSCT, n (%)	
Bone marrow/cord blood	31 (16.9)
Peripheral blood stem cells	152 (83.1)

ECP, extracorporeal photopheresis; HSCT, hematopoietic stem cell transplantation;

IQR, interquartile range; SD, standard deviation; Pts, patients

Table 2
ECP treatment pattern by follow-up year.

Follow-up year from index date	Number of patients exposed to ECP (total patients at risk)	Median (IQR 1–3) number of ECP treatments
1	112 (183)	11 (2–21)
2	82 (149)	16.5 (4–28)
3	44 (110)	15.5 (7–25)
4	32 (87)	14 (4–22)
5	22 (67)	20 (11–29)
6	11 (54)	7 (4–23)
7	7 (39)	15 (1–34)
\geq 8	5 (31)	13 (12–23)
Overall	183 (183)	18 (4–39)

ECP, extracorporeal photopheresis; IQR, interquartile range

Table 3
Proportion of patients treated with corticosteroids and/or immunosuppressive agents 3–0 months prior to ECP treatment initiation.

Patients	Cyclosporine, n (%)	Tacrolimus, n (%)	Ruxolitinib, n (%)	Prednisolone and/or prednisone, n (%)
183	165 (90.0)	18 (9.8)	7 (3.8)	96 (52.5)

ECP, extracorporeal photopheresis

18), ruxolitinib (n= 7), hydrocortisone, methylprednisolone or fludrocortisone (n= 4) or dexamethasone or betamethasone (n= 2) in the period 3–0 months prior to ECP initiation to enable post-ECP initiation treatment comparisons (Supplementary Table 1). The incidence rate of infections during the 3-month period prior to ECP initiation was 79.2% and decreased over time to 59.1% ([9–12 months after-ECP initiation] $p < 0.001$) (Table 5).

3.4. Healthcare resource utilization and cost

The average time spent in healthcare (inpatient and outpatient specialized care) declined over follow-up time after ECP initiation; from 68.9% to 22.1% in the first (n= 181) and fifth (n= 55) follow-up year after index, respectively (Table 6). The direct medical cost per patient-year decreased from €27,719 to €1,981 when comparing the first and fifth follow-up year after index (Table 6).

3.5. Sickness absence and productivity loss

Among patients $<$ 66 years (n= 130), sickness-associated time absent from work decreased from 73.2% to 31.9% in the first and fifth follow-up year, with a corresponding decrease in productivity loss from 20,358 euro to 7,211 euro per patient per year (Table 7).

4. Discussion

To our knowledge this is the first study which has investigated the association between ECP treatment and long-term outcomes, time spent in healthcare and patients' ability to return to work in cGVHD patients from a national-wide, real-world perspective.

First line treatment for moderate to severe cGVHD treatment is systemic immunosuppressive treatment with corticosteroids and immunosuppressant agents; usually prednisolone and often in combination with a calcineurin inhibitor [9,12,26]. However, with high rates of steroid refractory disease [9,27,28] and toxicity and morbidities associated with high dose steroids [10,29–31], a reduced need for immunosuppression is an important outcome to assess the benefit of immunomodulatory treatments such as ECP. A major finding from our study was that cumulative dose of prescribed prednisolone/prednisone was reduced by 41.3%, 6–9 months after initiation of ECP treatment compared to the 3-month period pre-ECP. This finding is in line with a previous study

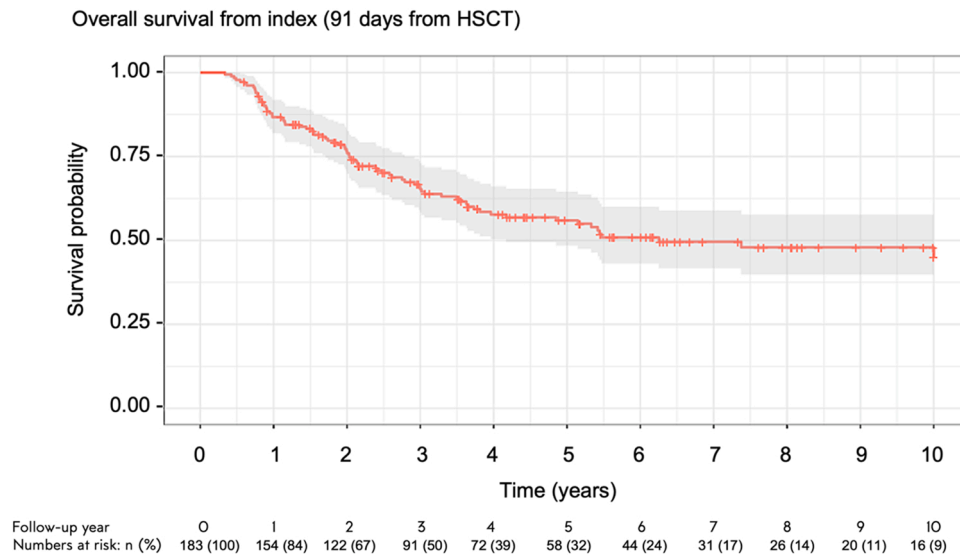


Fig. 1. All-cause survival analysis for HSCT patients exposed to ECP, from index 91 days post-HSCT.

Table 4
Cumulative dose of prednisolone/prednisone and cyclosporin associated with treatment initiation.

Time period	Patients, n	Patient-time (3 m)	Prednisolone / prednisone, mg (p-value)	Cyclosporin, mg (p-value)
3–0 months before first ECP	183	183	1381 (ref.)	12,242 (ref.)
0–3 months after first ECP	183	182	1064 (0.059)	6339 (<0.001)
3–6 months after first ECP	179	176	1117 (0.090)	5245 (<0.001)
6–9 months after first ECP	173	162	811 (<0.05)	4627 (<0.001)
9–12 months after first ECP	154	152	658 (<0.001)	3501 (<0.001)

ECP, extracorporeal photopheresis; mg, milligram; ref, reference.

Table 5
Infection rates associated with ECP treatment initiation.

Time period	Patients, n	Patient-time (3 m)	Patients with infection, n (%)	P-value
3–0 months before first ECP	183	183	145 (79.2)	ref
0–3 months after first ECP	183	182	135 (73.8)	n.s.
3–6 months after first ECP	179	176	121 (67.6)	< 0.01
6–9 months after first ECP	173	162	125 (72.3)	< 0.01
9–12 months after first ECP	154	152	91 (59.1)	< 0.01

ECP, extracorporeal photopheresis; mg, milligram; ref, reference; n.s., not significant

including Polish patients, which showed ECP treatment was associated with a reduction in prednisone dose from 0.32 mg to 0.07 mg per kg bodyweight and complete steroid discontinuation in 6 of 13 patients [32]. Similarly, a Spanish multicenter study showed that reduction in

Table 6
Average time spent in healthcare and associated direct medical cost.

Follow-up year	Patients, n	Patient-time (years)	Percentage of time spent in healthcare, %	Cost per patient-year (euro)
1	183	163 ^a	68.9	27,719
2	149	131	40.7	13,781
3	110	98	31.2	3,744
4	87	77	25.0	1,877
5	67	61	22.1	1,981

^a Patient-years for medical cost is based on n = 163, since DRG codes used to calculate direct medical cost were available only until December 2019.

Table 7
Sickness absence and productivity loss among ECP-treated patients < 66 years.

Follow-up year	Patients, n	Patient-time (years)	Proportion of time with sickness absence (%)	Productivity loss (euro)
1	130	124	73.2	20,358
2	115	100	61.9	17,416
3	85	73	52.2	14,450
4	64	54	45.0	11,435
5	48	42	31.9	7211

steroid therapy after ECP treatment was associated with improved overall survival rates [33]. Overall, these findings for ECP support the overarching objectives for effective cGVHD treatments to enable steroid tapering.

We further assessed the need for other immunosuppressive agents after ECP treatment initiation. The cumulative prescribed dose of cyclosporin decreased 3 months after ECP initiation by 48.2% compared to the 3-month period pre-ECP. Too few patients received tacrolimus and ruxolitinib for meaningful comparisons, however a trend toward similar or increased usage, respectively, was observed. Increased ruxolitinib over time may be reflective of the only recent EMA approval for cGVHD [34]. Similarly with hydrocortisone, methylprednisolone and fludrocortisone, an increase may be associated with use in later stages of cGVHD therapy, however with so few patients, larger patient numbers would be required for meaningful conclusions.

Infection is a severe problem associated with immunosuppression [35], but immunosuppression is important to prevent or reduce the severity of cGVHD. A systematic review of adverse events associated

with cGVHD treatments indicated infection was the most commonly reported adverse event, and ECP was associated with the lowest observed incidence of treatment-attributable infections and laboratory abnormalities [36]. Similarly, a recent US claims study reported 97% of GVHD patients had at least 1 steroid-associated complication within the first two years after diagnosis, and that infection was the most common complication (79.5%) [37]. Furthermore, patients with an infection experienced the highest hospitalization rate and highest associated healthcare cost. In the current study we observed a decreased incidence of infections after initiation of ECP treatment; an important finding as effective cGVHD treatments should have a minimal side effect profile. All-cause time in specialized care decreased over time among ECP-treated patients, as did associated healthcare costs. The major factor associated with this decrease was the reduction in time spent in inpatient care (42% vs 6% of the year spent in inpatient care in the first and fifth follow-up years, respectively, compared to 31.5% vs 16% associated with outpatient visits). While we did not specifically quantify infection-associated HRU from the registers, the association between decreased all-cause HRU burden over time and lower rates of infection among the ECP-treated cGVHD patients is in line with findings from the US study [37]. However, despite a median OS of 6 years, mortality of the sickest patients in the earlier follow-up periods may also contribute to annual costs being lower for cGVHD patients after 5 years post HSCT.

A unique component of this study is the addition of understanding of the broader societal costs by examining the burden of workplace productivity loss. cGVHD is a potentially debilitating complication and economic costs associated with patients' inability to work are significant. In the United States it was estimated that only 37.5% of cGVHD patients would return to work, which was predicted to total to approximately 605,631 years' worth of lost income [25]. This was estimated to cost five-times more than the 10-year cost of treating the condition [25]. To our knowledge, the current study is the first to analyze sickness absence and productivity loss associated with ECP-treated cGVHD patients. The finding that patients' sickness absence reduced from 73.2% in the first year to 31.9% in the fifth follow-up after HSCT is in line with our other findings of less time spent in healthcare and a lesser burden of infections.

Furthermore, return to work after illness/injury has been shown to be associated with improved quality of life (QoL) outcomes for patients [38,39]. This is of relevance to cGVHD patients, where QoL impact is significant [40], and ECP treatment has been reported to improve QoL in steroid refractory cGVHD patients [23,41]. In a randomized clinical trial, Flowers et al. reported greater improvement of QoL associated with ECP among cGVHD patients, attributed to both betterment of the disease status and a reduction in corticosteroid use [23]. Similarly, Dignan et al. reported improved QoL scores among 17 out of 18 cGVHD patients treated with ECP [41]. While QoL was not measured in our study, the finding of reduced time spent in healthcare and a greater ability to return to work are positive outcome for ECP-treated cGVHD patients that may lead to QoL improvements.

Regarding direct medical costs, previous studies have suggested the cost-effectiveness of ECP for the treatment of cGVHD. A modeling study in Spain simulating third-line strategies for cGVHD suggested that despite higher initial acquisition costs for ECP, ECP would be more cost effective compared to imatinib after 9 months and rituximab after 5 years [42]. Similarly, Italian and Australian modeling studies have similarly reported lower medical costs associated with ECP [43,44]. In a previous register study in Sweden, HRU cost was assessed for moderate-severe cGVHD patients; encompassing both ECP-treated patients and those treated with pharmacological agents. That study showed that the mean cumulative three-year HRU cost for moderate-severe cGVHD patients who survived 6-month post HSCT was €65,559 [14]. While not directly comparable, that was higher than the current finding for ECP-treated cGVHD patients in the same time period (€45,244).

Finally, our current finding of a median 7.8 months from index date to first ECP treatment is similar to the average 5.4 months from cGVHD diagnosis reported in a US claims database study [24]. In terms of survival, an approximate 85% 1-yr OS was also similar to a Danish single-site study which reported 94% 1-year OS among moderate-severe ECP treated patients after cGVHD diagnosis [45]. A strength of this study is that we were able to assess long term survival; reporting a median OS of 6 years for cGVHD patients treated with ECP. This is in line with other studies showing favorable OS associated with ECP, including in acute cGVHD [46], systemic sclerosis [47], HSCT patients with bronchiolitis obliterans [48] and cutaneous T-cell lymphoma [49]. With the use of ECP in line with the recommendations, and results similar to other real-world studies, the current findings have applicability to other countries where ECP guidelines and use are similar.

5. Limitations

While strengths of the current study include the long-term, population-wide scope and linkage of comprehensive clinical characterization and health economic outcomes, this is a descriptive retrospective study and register data has limitations in terms of clinical data granularity. Underreporting of cGVHD diagnoses recorded in the Patient Register made this unreliable to establish cGVHD start date, and that the proxy of 91 days post HSCT as index date meant only an estimation of time to ECP initiation from cGVHD manifestation could be included. While the time period was selected to limit inclusion of acute GVHD cases, some cases with late presentation may not have been excluded. Similarly, steroid use associated with acute cGVHD treatment may contribute to our pre-ECP cGVHD treatment analyses. We acknowledge the MAGIC criteria/NIH 2014 criteria would have been of value for defining the patient population [6]. Furthermore, we were unable to determine cGVHD severity with enough sensitivity to enable outcome comparisons between moderate-severe cGVHD patients treated with and without ECP. To employ a similar treatment-based severity classification strategy as used in a recent Swedish study [14] ran the risk of bias by indication, as ECP itself is associated with selection of the patient group with the most severe disease. Therefore, we have performed intra-patient comparisons of cGVHD patients pre- and post-ECP initiation to offer insight into the longitudinal treatment patterns of ECP in the real-world.

The definition for infections was based on records of diagnoses and drug treatment proxies aimed to distinguish between prophylaxis and treatment, and while it was designed to reflect clinical care practice, it may be subject to the limitations inherent in registry-based analyses. Limitations also include that drugs administered in hospital are not reliably captured, and therefore our dose analyses are derived from pharmacy dispensation records. Some patients with severe cGVHD may have received additional high-dose steroids or other immunosuppressant agents in hospital which are not reflected in the Prescribed Drug Register. HRU assessment includes specialized hospital care (inpatient and outpatient), however primary care is not included in the Patient Register. For time in outpatient care analysis each record is counted as one day, which may lead to an overestimation of time patients specifically spend within the healthcare system. Similarly, DRG-based costing estimates exclude costs associated with primary care and pharmacy dispensed medicines.

6. Conclusions

The current study utilizes a unique, longitudinal population-based dataset in Sweden that enabled a broad characterization of clinical and health economic outcomes associated with ECP treatment in clinical practice. This study contributes important clinical insights regarding the utility of ECP to treat cGVHD among patients who underwent HSCT, ultimately supporting better outcomes for cGVHD patients and reduced HRU and cost burden for society. Future studies might consider differentiating between moderate and severe cases to assess the effects on ECP

in these different cGVHD severity states.

Funding sources

Mallinckrodt was the sponsor of the study.

CRediT authorship contribution statement

FS: Conceptualization and design, Formal analysis and methodology, Investigation and interpretation, Project administration, Writing - original draft, Writing - review & editing. **CB:** Data curation, Formal analysis and methodology, Writing - review & editing. **TL:** Data curation, Formal analysis and methodology, Writing - review & editing. **SF:** Data curation, Formal analysis and methodology, Writing - review & editing. **MR:** Conceptualization and design, Formal analysis and methodology, Investigation and interpretation, Writing - review & editing. **OB:** Conceptualization and design, Investigation and interpretation, Writing - review & editing. **JD:** Conceptualization and design, Investigation and interpretation, Writing - review & editing. **TE:** Conceptualization and design, Investigation and interpretation, Writing - review & editing. **CJ:** Conceptualization and design, Project administration, Writing - original draft, Writing - review & editing. **JM:** Conceptualization and design, Investigation and interpretation, Writing - review & editing. **GB:** Conceptualization and design, Formal analysis and methodology, Investigation and interpretation, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Frida Schain is an employee and own stocks in Schain Research AB. Christina Jones in an employee of Schain Research AB. Constance Boissin, Tamas Laczik and Stefano Fedeli have been interns at Schain Research AB and have received payments for analytical work. Schain Research AB has received payment from Mallinckrodt for work related to the study. Mats Remberger, Ola Blennow, Josefina Dykes, and Torsten Eich have no competing interests. Jonas Mattsson has received lecture honorarium from Mallinckrodt. Gösta Berlin has received lecture honorariums from Mallinckrodt.

Acknowledgments

We acknowledge Dr Victoria Wycelsma (Schain Research AB) for providing publication support. We acknowledge the Swedish National Board of Health and Welfare and Sweden Statistics for excellent support with data extraction.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.transci.2023.103705](https://doi.org/10.1016/j.transci.2023.103705).

References

- Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transpl* 2003;9:215–33.
- Agh T, Csanadi M, Voko Z, Webb T, Jeyakumaran D, Trudeau J, et al. Humanistic burden of patients with chronic graft-versus-host disease - systematic literature review of health-related quality of life and functional status. *Expert Rev Hematol* 2019;12:295–309.
- Csanadi M, Agh T, Tordai A, Webb T, Jeyakumaran D, Sengupta N, et al. A systematic literature review of incidence, mortality, and relapse of patients diagnosed with chronic graft versus host disease. *Expert Rev Hematol* 2019;12:311–23.
- Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood* 2002;100:406–14.
- Socie G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late effects working committee of the international bone marrow transplant registry. *N Engl J Med* 1999;341:14–21.
- Schoemans HM, Lee SJ, Ferrara JL, Wolff D, Levine JE, Schultz KR, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transpl* 2018;53:1401–15.
- Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol* 2012;158:46–61.
- Wolff D, Fatobene G, Rocha V, Kroger N, Flowers ME. Steroid-refractory chronic graft-versus-host disease: treatment options and patient management. *Bone Marrow Transpl* 2021;56:2079–87.
- Lee SJ, Nguyen TD, Onstad L, Bar M, Krakow EF, Salit RB, et al. Success of immunosuppressive treatments in patients with chronic graft-versus-host disease. *Biol Blood Marrow Transpl* 2018;24:555–62.
- Flowers MED, Martin PJ. How we treat chronic graft-versus-host disease. *Blood* 2015;125:606–15.
- Saidu NEB, Bonini C, Dickinson A, Grce M, Inngjerdigen M, Koehl U, et al. New approaches for the treatment of chronic graft-versus-host disease: current status and future directions. *Front Immunol* 2020;11:578314.
- Wolff D, Gerbitz A, Ayuk F, Kiani A, Hildebrandt GC, Vogelsang GB, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transpl* 2010;16:1611–28.
- Arai S, Arora M, Wang T, Spellman SR, He W, Couriel DR, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the center for international blood and marrow transplant research. *Biol Blood Marrow Transpl* 2015;21:266–74.
- Schain F, Batyrbekova N, Liwing J, Baculea S, Webb T, Remberger M, et al. Real-world study of direct medical and indirect costs and time spent in healthcare in patients with chronic graft versus host disease. *Eur J Health Econ* 2021;22:169–80.
- Padmanabhan A, Connelly-Smith L, Aquí N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing committee of the American society for apheresis: the eighth special issue. *J Clin Apher* 2019;34:171–354.
- Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, Gennery AR, 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;177:287–310.
- Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European society for blood and marrow transplantation. *Lancet Haematol* 2020;7:e157–67.
- Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT. Extracorporeal photopheresis in the management of graft-versus-host disease. *Curr Oncol* 2014;21:e310–25 (Stem Cell Transplant Steering C).
- Knobler R, Arenberger P, Arun A, Assaf C, Bagot M, Berlin G, et al. European dermatology forum – updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. *J Eur Acad Dermatol Venereol* 2020;34:2693–716.
- Perseghin P, Marchetti M, Messina C, Mazzoni A, Carlier P, Perotti C, et al. Best practice recommendations in: (1) Peripheral blood stem cell mobilization and collection and (2) acute and chronic GvHD treatment using extracorporeal photopheresis. A joint effort from SidEM (Societa Italiana di Emaferesi e Manipolazione Cellulare) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo). *Transfus Apher Sci* 2013;48:195–6.
- Nygaard M, Wichert S, Berlin G, Toss F. Extracorporeal photopheresis for graft-versus-host disease: a literature review and treatment guidelines proposed by the Nordic ECP Quality Group. *Eur J Haematol* 2020;104:361–75.
- Greinix HT, Volc-Platzer B, Rabitsch W, Gmeinhardt B, Guevara-Pineda C, Kalhs P, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood* 1998;92:3098–104.
- Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008;112:2667–74.
- Joshi N, Luo L, Huang X, Mitri G, Lovelace B, Pham A, et al. Second line systemic treatments including extracorporeal photopheresis among patients with chronic graft versus host disease (cGVHD) in the United States, 2009-2016. *Blood* 2017;130:4490.
- Jones CA, Fernandez LP, Weimersheimer P, Zakai NA, Sharf M, Mesa OA, et al. Estimating the burden of cost in chronic graft-versus-host disease: a human capital approach. *J Health Econ Outcomes Res* 2016;4:113–8.
- Ruutu T, Gratwohl A, de Witte T, Afanasiev B, Apperley J, Bacigalupo A, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transpl* 2014;49:168–73.
- Foss FM, DiVenuti GM, Chin K, Sprague K, Grodman H, Klein A, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transpl* 2005;35:1187–93.
- Apisarnthanarax N, Donato M, Korbling M, Couriel D, Gajewski J, Giral S, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transpl* 2003;31:459–65.
- Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood* 1990;76:1464–72.

- [30] Inamoto Y, Flowers ME, Lee SJ, Carpenter PA, Warren EH, Deeg HJ, et al. Influence of immunosuppressive treatment on risk of recurrent malignancy after allogeneic hematopoietic cell transplantation. *Blood* 2011;118:456–63.
- [31] Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term systemic corticosteroid exposure: a systematic literature review. *Clin Ther* 2017;39:2216–29.
- [32] Ussowicz M, Musial J, Mielcarek M, Tomaszewska A, Nasilowska-Adamska B, Kalwak K, et al. Steroid-sparing effect of extracorporeal photopheresis in the therapy of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transpl Proc* 2013;45:3375–80.
- [33] Oarbeascoa G, Lozano ML, Guerra LM, Amunarriz C, Saavedra CA, Garcia-Gala JM, et al. Retrospective multicenter study of extracorporeal photopheresis in steroid-refractory acute and chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2020;26:651–8.
- [34] Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med* 2021;385:228–38.
- [35] Huang XJ. Current status of haploidentical stem cell transplantation for leukemia. *J Hematol Oncol* 2008;1:27.
- [36] Velickovic VM, McIlwaine E, Zhang R, Spelman T. Adverse events in second- and third-line treatments for acute and chronic graft-versus-host disease: systematic review. *Ther Adv Hematol* 2020;11. 2040620720977039.
- [37] Bell EJ, Yu J, Bhatt V, Bunner SH, Lal LS, Galvin J, et al. Healthcare resource utilization and costs of steroid-associated complications in patients with graft-versus-host disease. *Transpl Cell Ther* 2022.
- [38] Materne M, Strandberg T, Lundqvist LO. Change in quality of life in relation to returning to work after acquired brain injury: a population-based register study. *Brain Inj* 2018;32:1731–9.
- [39] van Ditschuijzen JC, van Lieshout EMM, van Beeck EF, Verhofstad MHJ, den Hartog D. Health-related quality of life and return to work 1 year after major trauma from a network perspective. *Eur J Trauma Emerg Surg* 2021 (Dutch Trauma Registry S).
- [40] Lee SJ, Kim HT, Ho VT, Cutler C, Alyea EP, Soiffer RJ, et al. Quality of life associated with acute and chronic graft-versus-host disease. *Bone Marrow Transpl* 2006;38:305–10.
- [41] Dignan FL, Aguilar S, Scarisbrick JJ, Shaw BE, Potter MN, Cavenagh J, et al. Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. *Bone Marrow Transpl* 2014;49:704–8.
- [42] Crespo C, Perez-Simon JA, Rodriguez JM, Sierra J, Brosa M. Development of a population-based cost-effectiveness model of chronic graft-versus-host disease in Spain. *Clin Ther* 2012;34:1774–87.
- [43] de Waure C, Capri S, Veneziano MA, Specchia ML, Cadeddu C, Di Nardo F, et al. Extracorporeal photopheresis for second-line treatment of chronic graft-versus-host diseases: results from a health technology assessment in Italy. *Value Health* 2015;18:457–66.
- [44] Peacock A, Dehle F, Mesa Zapata OA, Prince HM, Gennari F, Taylor C. Cost-effectiveness of extracorporeal photopheresis for the treatment of patients with erythrodermic (Stage T4, M0) cutaneous T-cell lymphoma in the Australian setting. *Value Health* 2022;25:965–74.
- [45] Nygaard M, Karlsmark T, Andersen NS, Schjodt IM, Petersen SL, Friis LS, et al. Longitudinal follow-up of response status and concomitant immunosuppression in patients treated with extracorporeal photopheresis for chronic graft versus host disease. *Bone Marrow Transpl* 2019;54:35–43.
- [46] Solh M, Solomon S, Bashey A, Morris L, Farnham C, Zhang X, et al. Extracorporeal photopheresis (ECP) improves overall survival in the treatment of steroid refractory acute graft-versus-host disease (SR aGVHD). *Transplant Cell Ther Meet* 2021.
- [47] Gambichler T, Ozsoy O, Bui D, Scheel CH, Susok L. Preliminary results on long-term follow-up of systemic sclerosis patients under extracorporeal photopheresis. *J Dermatol Treat* 2021:1–4.
- [48] Hefazi M, Langer KJ, Khera N, Adamski J, Roy V, Winters JL, et al. Extracorporeal photopheresis improves survival in hematopoietic cell transplant patients with bronchiolitis obliterans syndrome without significantly impacting measured pulmonary functions. *Biol Blood Marrow Transpl* 2018;24:1906–13.
- [49] Knobler R, Duvic M, Querfeld C, Straus D, Horwitz S, Zain J, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. *Photodermatol Photoimmunol Photomed* 2012;28:250–7.