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Analysis of extracorporeal photopheresis within the frame of the WAA register

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ABSTRACT

The aim of the study was to investigate safety and if extracorporeal photopheresis (ECP) may change health criteria (HC) and quality of life (QoL).

Material and method: 560 patients (33 % women) were treated with ECP for a total of 13,871 procedures during a 17-years period. Mean age was 48 years (±18, range 3–81 years). Self-estimation of QoL was graded: 0 (suicidal) up to 10 (best ever) and HC: 0 (Bed ridden, ICU condition) up to 10 (athletic). Adverse events were analyzed. ANOVA and paired comparisons were performed.

Results: Patients were treated due to graft versus host disease (GVHD, n = 317), skin lymphoma (n = 70), solid organ transplants (n = 47), skin diseases (n = 20) and other diseases (n = 106). Adverse events (AEs) were registered in 5.4 % of the first treatments and in 1.2 % of the subsequent procedures. Severe AEs were present in 0.04 % of all procedures. No patient died due to the procedure. Tingling and stitching were the most common AE. For those with GVHD an improvement was noticed within approximately 10 procedures of ECP in the severity stage, QoL (from a mean of 6.1 to 6.8, $p < 0.002$) and the HC (6.1 -> 6.4, $p < 0.014$) and improved further with added procedures.

Conclusion: Photopheresis is an established therapy with few side effects. The present study of soft variables indicate that GVHD shows benefits upon ECP within approximately 10 procedures in regard to the severity of mainly skin GVHD, and lower baseline levels of HC and QoL.

1. Introduction

Extracorporeal photopheresis (ECP) is a cell-based immunotherapy that involves the reinfusion of autologous leukocytes after exposure to psoralen and UVA [1,2]. The therapeutic mechanisms triggered by ECP involve immunological effects. These effects may at least to some extent depend on the type of disease [1]. ECP can be performed either as an "offline" system where the apheresis, photo-activation and re-infusion procedures are performed in different devices, or an "in-line" system, where the procedures are integrated [3].

The reinfused cells will activate therapeutic mechanisms that involve immunostimulatory, immunosuppressive, and immunotolerizing effects [1]. These effects are used to treat patients that suffer from various diseases such as Sézary syndrome, cutaneous T-cell lymphoma, acute and chronic graft-versus-host disease (GVHD), atopic dermatitis and erythroderma of other origin [4–8]. ECP has also been investigated as a

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preventive measure to reduce rejection of solid organs transplants such as heart [9], lung [10], and kidney [11] transplant [1,6,5–8].

There are limited numbers of controlled studies and often inclusion criteria are quite strict [3]. Analysis of data from larger registers may add knowledge about therapies and patients.

The world apheresis association (WAA) has an established apheresis register [12] that is available since 2002 for any apheresis center to enter information about apheresis procedures (www.waa-registry.org). The register includes data on ECP [13,14]. It contains self-estimated information about quality of life (QoL) and health criteria (HC) [15].

The aim of the present study was to investigate data concerning ECP within the WAA register and if possible to find break-points in the change in HC and QoL after a certain number of procedures after start of ECP therapy.

2. Material and method

The WAA register comprises data of more than 100 000 apheresis procedures, collected from 44 centers in 17 countries (Sweden, Czech Republic, Austria, Lithuania, Belgium, the Netherlands, Germany, Italy, Portugal, Serbia, Macedonia, Australia, Republic of Croatia, Norway, South Africa, Turkey and Spain). Gender distribution for all treatments were 58 % men and 42 % women, mean age 53 ± 33 and 51 ± 37 years, respectively. This report focuses on patients treated with extra corporeal photochemotherapy (ECP) within the frame of the WAA apheresis register. All patients at each center were included in the ECP treatment based on local treatment policy. Self-estimation of quality of life (QoL) was made by the patients using grade 0 (suicidal) up to 10 (best ever) and Health Criteria (HC, Table 1) grade 0 (Bed ridden, ICU condition) up to 10 (athletic). Patients were asked for QoL in 5 centers and for HC in 7 centers. All patients that reported their QoL also reported the HC.

Data entry in the register includes information of age, gender, diagnosis, treatment procedure and devices used, anticoagulation, access used, replacement fluids used, and prophylactic medication given. Report of adverse events (AE) due to the procedure were registered and graded as mild (no need for medication), moderate (medication to ease symptoms), severe (interruption of the treatment procedure due to side effects) and if death occurred due to the treatment procedure. The term 'tingling and stitching' was used to describe the side effect of small muscular cramps and prickly sensations, usually described in relation with assumed hypocalcemia.

All ECP treated patients were divided into 5 groups based on indication (Table 2): Graft versus host disease (GVHD), solid organ transplant (SOT), skin lymphoma, skin disease and 'Other diagnoses'.

The register contains space for outcome criteria including if the patient lived or died during hospital stay or during the treatment procedure. However, such data was only filled out to a small extent.

The study was approved by the Ethics Committee in Umea (2011-113-31M). Data collection included informed consent from the patients.

Statistical analyses were made with group comparisons and paired comparisons for the same patient in longitudinal manner. ANOVA analyses according to the model of Tukey, non-parametric paired analyses Wilcoxon and non-paired Mann Whitney were used for comparison of variables between groups. When paired analyses of HC and QoL were performed the subsequent data of the same patient i.e., at procedure 2, 3, 4 and so on were compared to the baseline data at start of ECP and considered as a pair. Mean values and standard deviation (±), median and minimal-maximal values are given. A two tailed p-value of less than 0.05 was considered significant. Analyses were made using SPSS, IBM statistics (version 25). Multiple stepwise regression analyses were performed with either QoL or HC as dependent factor and as variables either HC or QoL and gender, age, weight of the patient, processed volume, number of procedures, and adverse events by degree (none, mild, moderate, severe).

GVHD was roughly graded based on organ/s involved, acute, chronic or compound, and according to severity score light (score 1), moderate (score 2), severe (score 3)[16].

Table 1
Grading of Health Criteria (HC) based on physical capacity.

Grade	Physical capacity
0	Patient is bedridden somnolent or under anesthesia (i.e., ICU)
1	Patient is bedridden, eats by him/herself
2	Can move out of bed
3	Is unable to fully manage toilette by him/herself
4	Is able to fully manage toilette by him/herself
5	Walks with a roller or sticks
6	Climbs > 1 stair or walks < 500 m
7	Climbs > 2 stairs or walks > 500 m
8	Active exercise (e.g. walks > 1 km / day)
9	Athletic exercise
10	Athletic competition

Table 2
Distribution of gender and various diagnoses as percentage of patients (N = 560) and as percentage of all ECP procedures (N = 13,871).

Diagnosis	Patients		Women	Procedures	
	N	%	%	N	%
GVHD	317	56.6	35	9144[b]	65.9
Skin lymphoma	70	12.5	23	1198	8.6
Solid organ Tx	47	8.4	32	861[a]	6.2
Skin disease	20	3.6	40	409	2.9
Other diseases	106	18.9	33	2259	16.3
Total	560	100	33.2	13,871	100

[a] Women received more procedures per capita (p = 0.013).
[b] Men received more procedures per capita (p = 0.015).

3. Results

During the period 2003 to November 2019 a total of 560 patients (33 % women) were given 13,871 ECP treatments. The mean age of the patients was 48 years (SD ± 18, range 3−81 years).

Table 2 shows the distribution of gender and five groups of indications for ECP. Most patients were treated due to GVHD (n = 317). In this report no differentiation was made between acute or chronic GVHD.

The definition of acute versus chronic GVHD and time intervals were well described in 15 versus 14 patients. The treatment period of ECP was at a mean 11 weeks (±16, 161 procedures in 15 patients) for acute versus 32 (±35, 452 procedures in 14 patients, p < 0.001) for chronic GVHD. A mean of 2.6 (±2.7, intervals of 152 procedures) procedures/week were performed for acute and 1.5 (±2.3, intervals of 440 procedures, p < 0.001) for those with chronic GVHD.

3.1. Adverse events (AEs)

Adverse events were registered in 2.1 % of all procedures (mild 0.4 %, moderate 1.7 %, severe 0.04 %) and includes 40 reports on problems with access or devices, i.e. in 0.3 % of the procedures. AEs were more common during the first treatment (5.4 %) and less in subsequent procedures (1.2 %). No patient died due to the ECP procedure. Over the latest years, a reduction in mild (p = 0.015, Spearman) and moderate AEs (p < 0.001) were noted (Fig. 1). In Table 3 the extent and degree of AEs are given in relation to the treatment indication. In Table 4 specific symptoms and degree of adverse event are given. Tingling and stitching were the most common side effects.

Table 5 displays AEs with devices where more than 400 procedures had been performed. Cobe Spectra (Terumo BCT) and Optia (Terumo BCT) had the highest incidence of AEs.

Added devices to the main device, if used, were of no significance for AEs.

The distribution of anticoagulation used and related AEs in such

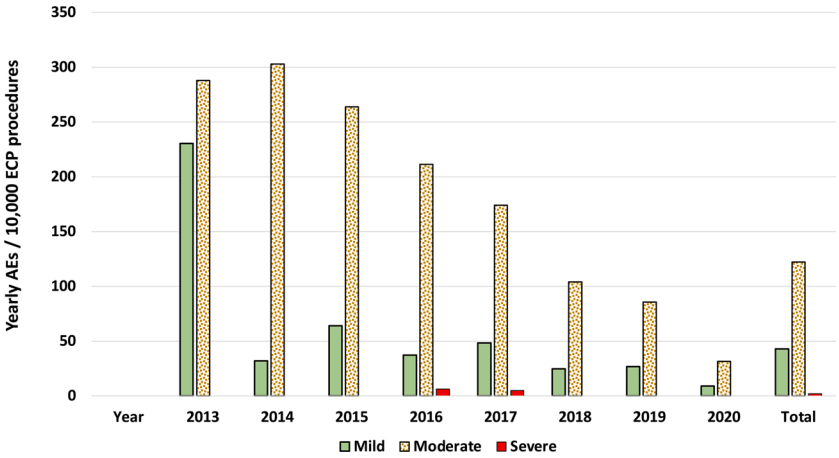

Fig. 1. Distribution of AEs, including years containing more than 600 (year 2013) and 1000 procedures (2014-). The yearly incidence of AEs are given as episodes/10,000 procedures.

Table 3
Distribution of various groups of indication for ECP and degree, incidence and gender differences of AEs.

	Total AE %	Mild %	Moderate %	Severe %	Gender differences p-value
GVHD	2.1	0.42	1.66	0.04	<0.001[a]
Skin lymphoma	0.7	0.59	0.08	0.00	n.s.
Solid organ Tx	1.7	0.48	1.21	0.00	<0.001[a]
Skin disease	2.7	0.00	2.69	0.00	0.03[b]
Other diseases	1.1	0.53	0.53	0.04	n.s.
Total material	2.12	0.42	1.66	0.04	Not assessed

[a] Grade Moderate: women worse.
[b] Grade Moderate: men worse.

Table 4
Percentage of various adverse events within each grade (excluding access and technical problems, n = 40).

	Severe (n = 3) %	Moderate (n = 180) %	MILD (n = 27) %
Bronchospasm	33.3		3.7
Gastrointestinal bleeding	33.3		
Chills and fever	33.3		3.7
Tingling and stitching*		86.7	29.6
Hypotension		5.5	18.5
Nausea and/or vomiting		1.1	7.4
Sepsis, late complication		0.55	
Abdominal pain		0.55	0.0
Muscle cramps in foot		0.55	
Arrhythmia			11.1
Thrombophlebitis due to puncture			3.7
Itching, late complication			3.7
Local bleeding after prior surgery			7.4

* Stitching – prickly sensation.

procedures are shown in Tables 6 and 7 respectively. Thereby ACD-A/B was associated with most AEs in relation to number of procedures while the use of heparin showed less AEs.

Two centers had most of the tingling and stitching AEs. In one of those centers the processed volume was larger in the group suffering from this side effect than those without (7932 ± 1696 mL versus 7448 ± 1420, n = 96 and n = 1777 respectively, p < 0.001) while in the other unit no difference in processed volume was present (1502 ± 7 vs 1664 ± 1090, n = 33 and 383 respectively). Women were more prone to suffer from the AE tingling and stitching (20 versus 6.6 episodes/1000 procedures, p < 0.001, RR 3.1 CI 2.2–4.2). Hypotensive AEs were observed in 15 procedures. The volumes processed were smaller in those with hypotension (5758 ± 1011 vs 6623 ± 1078, n = 13, p = 0.004). In 14 of 15 episodes these were present when collection was performed with the Cobe Spectra or Optia device before preparation and return. Most of those patients had acute GVHD. The patients suffered from a severe gastrointestinal form of the disease, with hemorrhagic diarrhoea, anemia, and hemodynamic instability. The collections of mononuclear cells (MNC) were performed in the ICU, where the patients were treated. The patients had various clinical complications at the same time, and were in a higher risk of complications during apheresis. The hypotensive reactions were observed in patients in the course of mononuclear cells collections, not during reinfusion. The reactions were not severe and not life threatening, and were treated efficiently with administration of colloids or saline. Some of the patients had hypotensive reactions during repeated procedures.

Patients receiving i.v. calcium as prophylaxis to counteract side effects, showed an AE in 6 procedures of 1026 (0.6 %), versus 45 AEs of 6372 (0.7 %) procedures performed without prophylaxis (non-significant). Those who received oral Calcium tablets (approx. 1000 mg) as prophylaxis suffered from more episodes of AEs, all moderate (25 of 330 procedures, 7.6 %) versus those without prophylaxis (47 moderate and 1 severe; p < 0.001, RR 10.0 CI 6.2–16). Most of the AEs with tablets were tingling and stitching (85 %). In patients prescribed prophylaxis by oral calcium only notes revealed that several of these patients were prescribed additional iv calcium, due to hypocalcemia (lab. value).

The distribution of anticoagulation used and related AEs in such procedures are shown in Tables 6 and 7 respectively. Thereby ACD-A/B was associated with most AEs in relation to number of procedures while the use of heparin showed less AEs.

The weight of the patients did not differ between those who suffered from AEs versus those without (Table 8), while the height and processed volumes differed (Table 8).

3.2. Quality of Life (QoL) and Health Criteria (HC)

3.2.1. Group comparisons

Self-estimated QoL were performed in 3376 procedures and estimates of HC during 8516 procedures. The initial mean values of the QoL and HC are given in Tables 9 and 10.

QoL for GVHD patients improved significantly within 10 procedures. Group comparison (ANOVA) showed a significant improvement in QoL for GVHD patients from start to after more than 10 procedures (6.1 ± 1.8

Table 5
Distribution of AEs (in %) for the 6 most frequently used apheresis devices and number of procedures (N) and statistical comparisons (relative risk: RR, confidence interval: CI, not significant: n.s.) with Haemonetics chosen as reference due to least AEs.

AE	Cobe Spectra Terumo BCT	Spectra Optia Terumo BCT	Therakos Cellex	Therakos UVAR	MCS9000 Haemonetics	Amicus Fresenius
N	1961	2359	3824	1407	2899	415
Mild, %	0.61	0.76	0.52	0.64	0	0.24
Moderate, %	4.23	3.52	1.80	0.14	0.10	0
Severe, %	0.05	0.04	0.03	0.14	0	0
Total, %	4.90	4.32	2.35	0.92	0.10	0.24
Mild AE RR (CI)	18 (2–142)	22 (3–167)	15 (2–112)	18 (2–146)	Reference	n.s.
Moderate	41 (13–130)	7.8 (13–130)	17 (5–54)	n.s.	Reference	n.s.

Table 6
Anticoagulation in relation to grade of AEs. Comparison between ACD-A/B (either of ACD-A or ACD-B) and heparin is shown. Risk Ratio (RR) and confidence interval (CI) are given. ACD-B contains 1.3 % citrate.

AE	ACD-A/B	ACD-A	Heparin	ACD +heparin	ACD-A/B versus heparin p-value
N=	11,257	690	1323	401	
Mild	0.43	0.14	0.76	0.25	n.s.
Moderate	1.59	0.29	0.15	0.00	<0.001, RR 10, CI 2.6–42
Severe	0.03	0.00	0.15	0.00	0.035
Total %	2.04	0.43	1.06	0.25	

vs 7.0 ± 1.0, p = 0.01) was further improved after additional procedures (Fig. 2); and in SOT after more than 50 procedures (p = 0.017), while no significant change was found for patients in the group 'Skin lymphoma' and 'Other diseases'. For skin diseases only one of 5 patients had data on QoL.

QoL was related to the estimation of the HC such as for GVHD (rho = 0.67, p < 0.001, N = 970), Solid organ rejection (rho = 0.74, p < 0.001, n = 118), and skin lymphoma (rho = 0.59, p < 0.001, n = 271).

Multiple stepwise regression models revealed for HC as dependent variable and for GVHD an R-square of 0.51 (p = 0.030, n = 2026) related to the variables QoL, women as gender, younger age, processed volume, number of procedures and weight; This means that patients that have a higher HC also have a higher QoL, are younger and ECP is performed using larger volumes, performing a larger number of ECP procedures and having a greater weight.

Multiple stepwise regression models revealed for HC as dependent variable and for skin lymphoma R-square 0.50, (p < 0.001, n = 271) was related to QoL and male gender. This means that HC is higher in those with higher QoL and more in male gender.

No analyses were possible of solid organs or skin disease since the numbers QoL and HC reports were too few (n = 3 versus n = 0). Multiple stepwise regression with QoL as dependent factor: for those with GVHD retained HC, number of procedures, better for women and age with R-square 0.52, p = 0.004 in the model; This means that QoL was higher in those with a greater HC, who performed more ECPs, being women and of older age.

Multiple stepwise regression with QoL as dependent factor: For skin lymphoma (n = 270) R-square 0.50, p < 0.001 including the variables HC and processed volume. This means that QoL was related to HC and larger processed volumes.

Table 9
Patient self-estimation of HC, and QoL at first occasion. Mean values, number of patients at first estimate (N). QoL was reported by a part of the patients that reported their HC.

	Health condition		Quality of Life	
Therapy Groups	N	Mean ± SD	N	Mean ± SD
GVHD	212	6.1 ± 1.8	55	6.2 ± 1.4
Skin lymphoma	59	6.1 ± 1.4	9	7.1 ± 0.6
Solid organ Tx	40	6.3 ± 1.5	19	6.8 ± 1.5
Skin	5	6.2 ± 0.4	1	7.0
Other diagnoses	38	6.3 ± 1.8	19	6.8 ± 1.5

Table 7
Anticoagulation used in relation to the groups of ECP indication.

	Missing data	ACD-A/B	ACD-A	CPD-citrate	LMWH	Hep	ACD-A/B+ Hep	Total
GVHD	22	7239	436	6	16	1104	321	9144
Skin lymphoma	2	1007	66			69	54	1198
Solid organ Tx	7	678	124			32	20	861
Skin	0	409						409
Other	7	2039	68		2	137	6	2259

LMWH: Low Molecular Weight Heparin; Hep: heparin.

Table 8
Comparison of distribution of height (in cm) and processed volume (in ml) between various grades of adverse events. Severe AEs are excluded due to few observations.

		Height, cm			Processed volume, ml		
		No AE [1,2]	Mild AE	Moderate AE	No AE[3]	Mild AE[4]	Moderate AE
N	Valid	11,999	50	141	11,287	52	177
N	Missing	1477	11	43	2189	9	7
Mean		169	175	172	3111	2983	5289
Median		170	175	176	1524	1623	6200
Std. Deviation		14	12	9	3362	2770	3467

[1] No AE vs Mild: p-value<0.003.
[2] No AE vs Moderate: p-value<0.003.
[3] No AE vs Moderate: p-value<0.003.
[4] Mild AE vs Moderate: p-value<0.003.

Table 10
GVHD patients only. Paired comparison with the initial baseline ECP 1 and follow up grading of Health Criteria (given in Table 1) estimated by the patient at the different procedures of ECP (ECP). In non-paired comparison a limit for improved versus impaired outcome data was noted at grade 7 (Climbs > 2 stairs or walks > 500 m). Therefore, here the data was analyzed in two groups, one group with an initial grading of 0-6 and the other group with the grading 7 to 10.

	Health Criteria- Grade 0–6						Health Criteria- Grade 7–10					
	N pairs	Mean	SD	Median	Range	p-value	N pairs	Mean	SD	Median	Range	p-value
ECP 1	66	4.74	1.28	5	(1–6)		75	7.52	0.55	7	(7–9)	
ECP 2	66	4.77	1.38	5	(1–8)	0.49	75	7.43	0.79	7	(3–9)	0.096
ECP 3	66	4.85	1.37	5	(1–8)	0.243	75	7.31	1.00	7	(3–9)	0.028
ECP 4	66	4.98	1.42	5	(1–8)	0.031	74	7.22	1.01	7	(3–9)	0.003
ECP 5	66	4.92	1.47	5	(1–7)	0.076	74	7.23	1.03	7	(3–9)	0.011
ECP 6	66	5.08	1.51	5	(1–8)	0.013	73	7.26	0.89	7	(3–9)	0.008
ECP 7	64	5.23	1.66	5	(1–8)	0.003	74	7.32	0.97	7	(3–9)	0.073
ECP 8	64	5.2	1.68	5	(1–8)	0.003	74	7.32	1.01	7	(3–9)	0.083
ECP 9	62	5.4	1.65	5	(1–8)	<0.001	73	7.29	0.98	7	(3–9)	0.031
ECP 10	61	5.41	1.47	5	(1–8)	<0.001	72	7.26	0.96	7	(3–9)	0.01
ECP 11	56	5.57	1.26	5.5	(2–8)	<0.001	71	7.17	1.10	7	(3–9)	0.006
ECP 12	54	5.46	1.37	5	(1–8)	0.001	69	7.13	1.12	7	(3–9)	0.002
ECP 13	52	5.5	1.53	5	(1–8)	0.001	66	7.05	1.18	7	(3–9)	0.001
ECP 14	52	5.44	1.59	5	(1–8)	0.004	67	7.13	0.98	7	(3–9)	0.002
ECP 15	45	5.76	1.37	6	(2–8)	<0.001	64	7.08	1.16	7	(3–9)	0.002
ECP 16	42	5.76	1.36	6	(2–8)	<0.001	60	7.07	1.18	7	(3–7)	0.001
ECP 17	42	5.9	1.27	6	(3–8)	<0.001	57	7.11	1.35	7	(1–7)	0.009
ECP 18	41	5.9	1.34	6	(3–8)	<0.001	56	7.18	1.30	7	(2–7)	0.027
ECP 19	42	6.02	1.30	6	(3–8)	<0.001	55	7.35	1.21	8	(2–8)	0.344
ECP 20	41	5.98	1.28	6	(3–8)	<0.001	53	7.34	1.19	8	(2–8)	0.224
ECP 21	39	5.79	1.47	6	(1–8)	<0.001	53	7.19	1.16	7	(3–7)	0.013
ECP 22	37	5.86	1.49	6	(1–8)	<0.001	53	7.25	1.19	8	(3–8)	0.04
ECP 23	34	6	1.30	6	(4–8)	<0.001	52	7.15	1.07	7	(3–7)	0.003
ECP 24	35	5.8	1.51	6	(2–8)	0.002	51	7.06	1.22	7	(3–7)	0.002
ECP 25	31	5.68	1.66	5	(1–8)	0.006	50	7.22	1.20	7	(3–7)	0.032
ECP 26	31	5.65	1.58	5	(1–8)	0.006	50	7.18	1.22	7	(3–7)	0.018
ECP 27	27	6.15	1.29	6	(4–8)	0	49	7.06	1.25	7	(3–7)	0.005
ECP 28	27	6.11	1.37	6	(3–8)	0	48	7.17	1.26	8	(3–8)	0.017
ECP 29	27	5.96	1.37	6	(3–8)	0.001	47	7.28	1.17	8	(3–8)	0.141
ECP 30	27	5.89	1.42	5	(3–8)	0.001	45	7.38	0.98	8	(4–8)	0.29

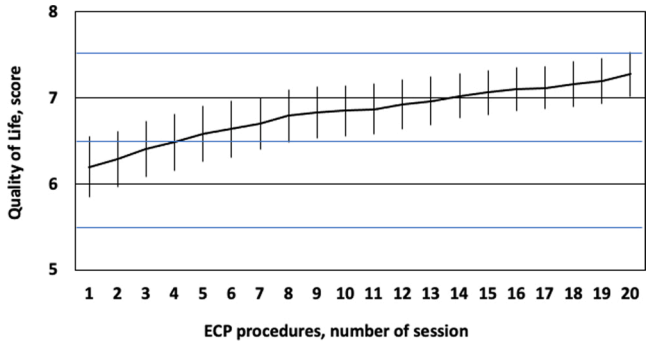

Fig. 2. Mean and confidence intervals of GVHD patient that reported quality of life in subjects with ≥ 20 ECP-treatments (n = 52).

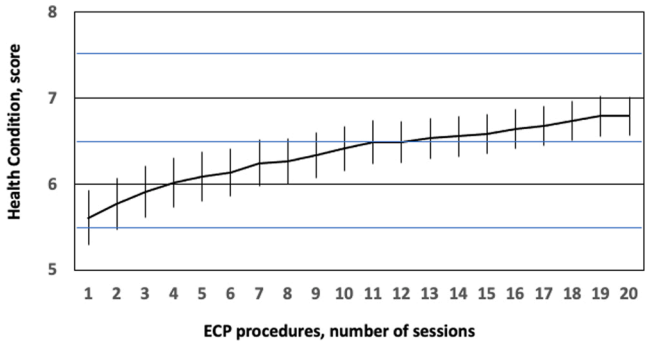

Fig. 3. Mean and confidence intervals of GVHD patient that reported health status in subjects with ≥ 20 ECP-treatments (n = 112).

Solid organs: too few (n = 618) R-square 0.66, p < 0.001 related to HC, male gender and younger age; Skin ECPs were too few to analyze.

For patients with GVHD the initial HC values improved significantly within 9 procedures and improved further with added procedures (Fig. 3).

When analyses were divided into those who had HC grade 1–4 at the first procedure a significant improvement was noticed within 10 and more procedures and when the first HC was 5 or 6 significant improvement was first noted after 20 treatments. For the first HC with a grade 7 estimate improvement was significant first after more than 100 procedures (5 patients) while for those with HC grade 8 a significant reduction was noted after 10 procedures (to a mean of 7.2 ± 1.5).

The HC improved after 50 or more procedures for SOT but did not change significantly for skin lymphoma (6.02, n = 56) and neither for various skin diseases (6.20, n = 5).

3.2.2. Paired statistical comparison (performed of GVHD only)

Table 10 shows data of GVHD patients that performed 6 or more ECP procedures that included information of HC. Paired analyses were also performed of GVHD patients in regard to QoL.

QoL was significantly improved at series 17–19 (n = 31 pairs, p = 0.035–0.013) followed by borderline p-values and again significant at series 30 (n = 21 pairs, p = 0.021).

When the baseline level was grouped into those with a start estimate between 1–6 the outcome increased significantly from series 9 (n = 29 pairs, from 5 to 6, p = 0.043 and further on to a QoL level of 7).

Women experienced a significantly increased QoL after 9 series (p = 0.021) while such improvement was not found for men (baseline values did not differ).

Adults between 22 and 49 years experienced improved QoL after 15 series (n = 19 pairs, P = 0.003). Children and young persons including 21 years (n = 15 pairs) and patients 50 years and older did not

experience a significant change (n = 20 pairs).

HC analyses of the whole group (n = 140 pairs at start) showed a significant improvement from series 18 (n = 97 pairs, p = 0.043 and continuously, p ≤ 0.006).

When the baseline level was grouped into those with a start estimate between 1−6 the outcome increased significantly at series 4 (n = 66 pairs, p = 0.031 and further on, Table 10). When baseline level was between 7−10 a certain loss in physical capacity appeared after 3 series (P = 0.028, Table 10).

HC was not differently altered by gender. There was no difference in HC levels between men and women within the different series. Baseline values were similar for men and women for HC.

Adults between 22 and 49 years experienced improved HC after 15 series (n = 44 pairs, P = 0.047). Children and young persons including 21 years (n = 20 pairs) and patients 50 years and older did not experience a change in HC (n = 66 pairs).

3.3. Severity grade of GVHD

In 24 patients with GVHD (20 mainly skin and 4 mainly gastrointestinal) collection of severity grade of the GVHD were performed over a prolonged period. A significant reduction in the grade of GVHD was observed after 9 procedures (Table 11).

4. Discussion

The present study showed that centers included in the WAA register performed ECP mainly in patients suffering from GVHD as well as some other diagnoses that are included in the ASFA guidelines [6]. The main finding of this study is that patients suffering from GVHD show significant improved QoL and HC after approximately 10 ECP procedures with focus of beneficial effect when a lower baseline level is present. Such significant beneficial effects could also be found when comparison of the severity grading of the GVHD was followed over time. However, the present study does not reveal the extent of patients that did not respond to ECP therapy or those who received shorter ECP periods.

Notable is that women experienced a significant improvement in QoL, that was not found for men. Women might be more aware than men of changes in their surrounding that interfere with QoL. The results may guide clinician not to expect too much raise in the QoL estimate in men versus women while they responded similarly regarding HC.

Regarding patients suffering from GVHD the HC and QoL showed significant improvements in the patients with a worse initial HC. Further studies should evaluate if those who had a better HC at baseline but worsened in HC while the severity score of GVHD improved did so due to i.e., less exercise or adverse drug effects while being part of a chronic ECP program.

A limitation is the lack of randomization of patients when analyzing outcome criteria. However, the paired comparison allows an estimate over time with the patient being its own control.

The criteria used in this study do not evaluate the immunologic efficacy of ECP but is only an indirect measure of the efficacy of the ECP procedures performed.

The register data of the present study miss sufficient information if the patient suffered from acute, chronic or combined GVHD and also in numerous cases miss information of severity score, type of GVHD and outcome data that would allow separate analyses.

The study in numerous GVHD patients lacks information if the patient died during the ECP period or ended ECP due to death related to the GVHD.

This observational study included data of all patients treated at each participating center. Treatment protocols may differ as well as devices used. Protocols are filled out differently based on local resources and also if the apheresis center performed therapy on the order of other clinicians or if the clinician themselves were responsible for apheresis, and had access to outcome data. Center differences may also appear mainly for mild AEs since in some centers very mild AEs are not registered while this may be done by others. However, the differences found helps to get indication of possible risk factors involved that may be further explored. Multiple regression analyses results may be interpreted with caution since results may vary unexpectantly dependent on variables entered and possible confounders added into the model.

During the latest years the register differentiated between prophylactic medical measures. A higher incidence of AEs during the first than later procedures has been suggested to be related to variables such as performing the first procedure without prophylaxis, besides that the patient takes notice of even discrete mild AEs. Another reason may be that a higher speed during the first procedure may increase risk for citrate and volume induced side effects. Such variables that may have been adjusted for during the subsequent procedures. Therefore, calcium supplementation as prophylaxis may be prescribed also due to previous AEs when performing procedures without calcium administration. This could explain why prophylactic calcium administered iv was not related to significantly less AEs than those procedures where patients did not receive prophylactic calcium administration. The increase in AEs when using oral calcium tablets as prophylaxis may well be due to too small doses or delayed intestinal absorption of calcium. In some of these patients the ionized calcium level was reported to be low and additional iv calcium was given. In the pharmacopeia the side effects for the calcium tablets reported in the present study are reported to occur ‘seldom’.

The data does not rule out that citrate by itself may contribute to the tingling and stitching AEs, while the secondary hypocalcemic effect by citrate may be another mechanism responsible for other specific AEs. The tingling and stitching seemed also to be related to devices used and the amount of anticoagulation used in the procedures. The speed of the procedures and in parallel the speed and dose of citrate administration has not been controlled for in these data. Extracorporeal volumes besides the change from separate into integrated procedures may explain that differences in adverse events are seen over time.

Severe adverse events are rare and no patient died as a consequence of the procedure. For some diagnoses, women were more prone to suffer from AEs while for other AEs men were more common.

It should be pointed out that this a retrospective analysis of ECP data reported to the WAA register from 11 centers in 6 countries. The findings should be interpreted with caution as various devices are used for ECP

Table 11
Estimate of GVHD severity at each procedure during prolonged treatment periods in 24 patients. Outcome data at each separate patient data was estimated at each procedure and was compared with the baseline estimate (non-parametric Wilcoxon paired analysis). Four of the patients had gastrointestinal GVHD while the others had mainly skin GVHD. Severity grading was light (score 1), moderate (score 2), severe (score 3) [16].

	N pairs	Mean	SD	Median	p-value
Procedure 1	24	2.50	0.44	2.5	
Procedure 2	24	2.42	0.46	2.5	0.285
Procedure 3	24	2.35	0.54	2.5	0.121
Procedure 4	24	2.35	0.58	2.5	0.196
Procedure 5	24	2.40	0.59	2.5	0.427
Procedure 6	24	2.38	0.65	2.5	0.371
Procedure 7	24	2.23	0.62	2.25	0.04
Procedure 8	24	2.32	0.53	2.5	0.106
Procedure 9	24	2.21	0.67	2.25	0.011
Procedure 10	24	2.13	0.68	2.25	0.004
Procedure 11	24	2.26	0.65	2.5	0.048
Procedure 12	24	2.16	0.69	2.5	0.012
Procedure 13	22	1.97	0.67	2	0.002
Procedure 14	21	1.95	0.63	2	0.003
Procedure 15	21	1.95	0.68	2	0.002
Procedure 16	21	2.00	0.63	2	0.005
Procedure 17	19	1.92	0.67	2	0.004
Procedure 18	19	1.82	0.77	1.5	0.001
Procedure 19	19	1.92	0.67	2	0.002
Procedure 20	19	2.05	0.62	2	0.007

(in-line and off-line systems) with different blood volumes processed and the use of anticoagulants and calcium substitution varies between centers. The results may also be biased by differences in the routine of reporting AEs so that mainly mild but also moderate AEs might be underreported from some centers. On the other hand, we report data from a large number of consecutive and unselected ECP procedures and the findings will hopefully lead to further investigations.

Although not clearly divided between acute or chronic GVHD for analysis – the impression of the authors is that patients with severe acute GVHD represent a relatively sensitive group of patients, with increased potential to develop adverse reactions in the course of apheresis procedure. Such patients seem to have a higher risk of adverse reactions and urge for more intense surveillance.

5. Conclusion

Photopheresis is an established therapy with few adverse events. The present data indicate that GVHD patients with a lower baseline level of QoL and HC seem to increase their level most by ECP and the severity grade improved within 10 procedures.

CRediT authorship contribution statement

Blaha Milan: Conceptualization, Methodology, Writing, draft preparation, Data curation, Investigation, Analysis, Validation, Editing, Reviewing. **Gasova Zdenka:** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Berlin Gösta;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Audzijoniene Judita;** Conceptualization, Methodology, Data curation, Editing, Reviewing. **Griskevicius Antanas;** Conceptualization, Methodology, Data curation, Editing, Reviewing. **Dykes Josefina;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Bhuiyanova Zdenka;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Lanska Mirka;** Data curation, Investigation, Validation, Editing, Reviewing. **Eich Torsten;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Vrielink Hans;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Witt Volker;** Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Cengiz Seval Güldane;** Data curation, Investigation, Validation, Editing, Reviewing. **Ilhan Osman;** Methodology, Data curation, Investigation, Validation, Editing, Reviewing. **Stegmayr Bernd:** Conceptualization, Methodology, Data curation, Data Analysis, Investigation, Validation, Draft preparation, Editing, Reviewing.

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