La fotoaferesi terapeutica nel paziente pediatrico

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Fondazione IRCCS Policlinico San Matteo-Pavia-

Bologna, 4 ottobre 2023

XLVIII CONGRESSO NAZIONALE AIEOP

Bologna
2-4 Ottobre 2023

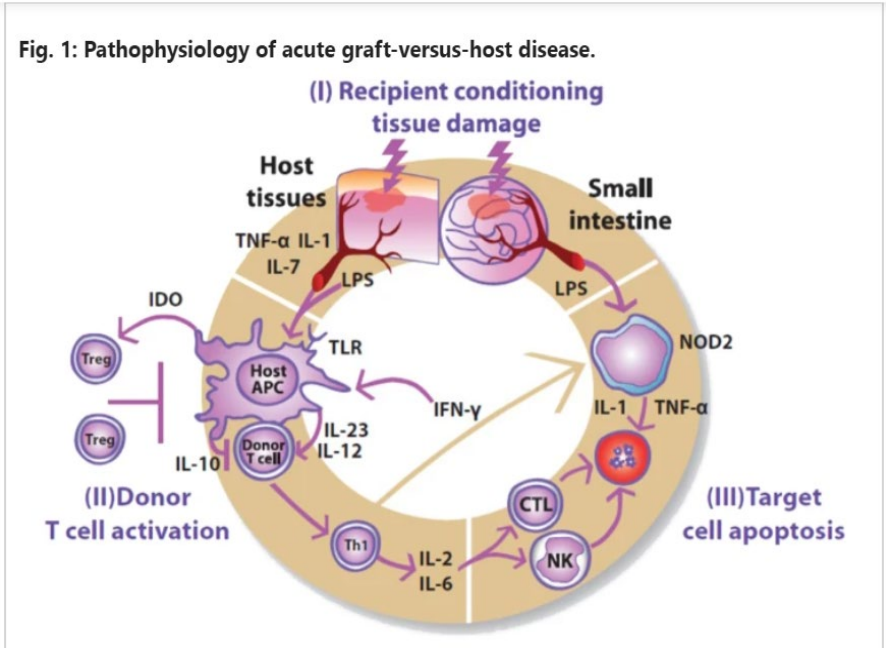
Il sottoscritto Claudia Del Fante

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

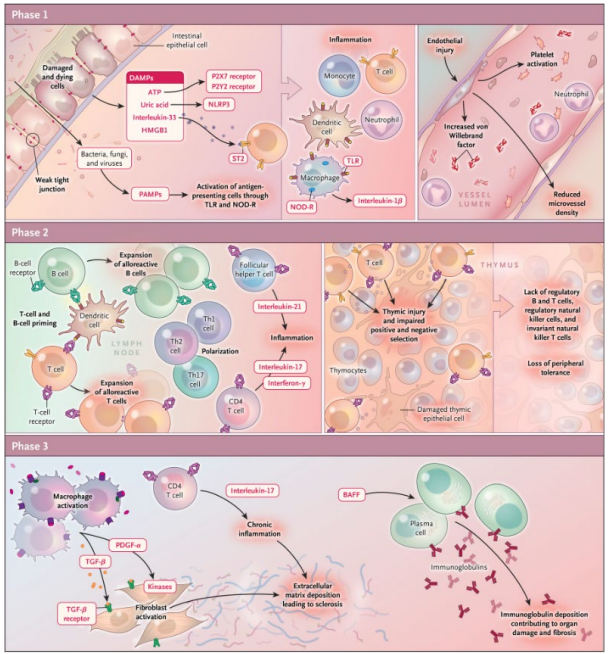
dichiara

❑ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

aGvHD and cGvHD are a multisystem disease



cGvHD



Acute inflammation & tissue injury

Chronic inflammation & dysregulated immunity

Aberrant tissue repair & fibrosis

Zeiser R, New Engl J Med 2017

GvHD is cause of morbidity (infections) and NRM in longer survival (cGvHD)

Steroids are the standard first line treatment for GvHD

Steroid refractory GvHD

NR: ≈50% pts

A wide range of second-line and subsequent lines of therapies are
recommended for SR GvHD with **disappointing results**

Main side effects of immunosuppressive therapy

Infections

Multiorgan failure

Retarded growth

Tumors

Low quality of life

Pediatric pts!

Management of SR acute and chronic GvHD

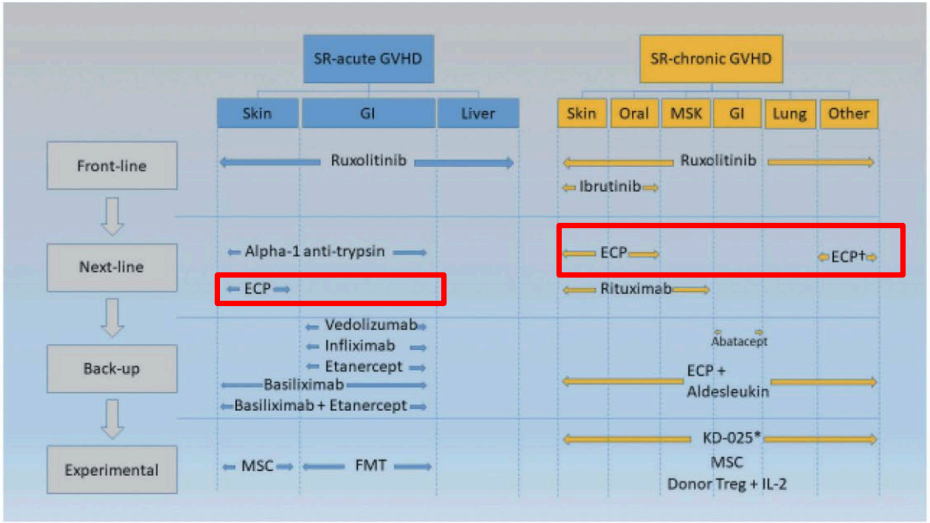


Figure 1. Suggested approach to the management of steroid-refractory (SR) acute and chronic GVHD.

Arrows represent the availability of evidence for efficacy of a therapy for a particular organ manifestation of SR-acute or SR-chronic GVHD. The order of therapy selection reflects the evidence outlined in the current review but does not imply a strict order. For example, there is no strict guidance to choose Vedolizumab before Infliximab for gut SR-acute GVHD, but one may choose to use alpha-1-antitrypsin before Vedolizumab for this condition. The absence of arrows for a particular experimental therapy suggests ongoing study without clear evidence of organ-specific efficacy. †ECP has been suggested to have efficacy in ocular and hepatic chronic GVHD as well. *KD-025 is still considered an experimental therapy at the time of this publication, but may soon receive FDA approval for the treatment of SR-chronic GVHD that has been refractory to at least two lines of therapy. Abbreviations: ECP, extracorporeal photopheresis, MSC, mesenchymal stem cells, FMT, fecal-microbiota transfer, Treg, regulatory T-cells, IL-2, interleukin-2.

ECP is a large-scale cell therapy

Approved in 1988 for CTCL

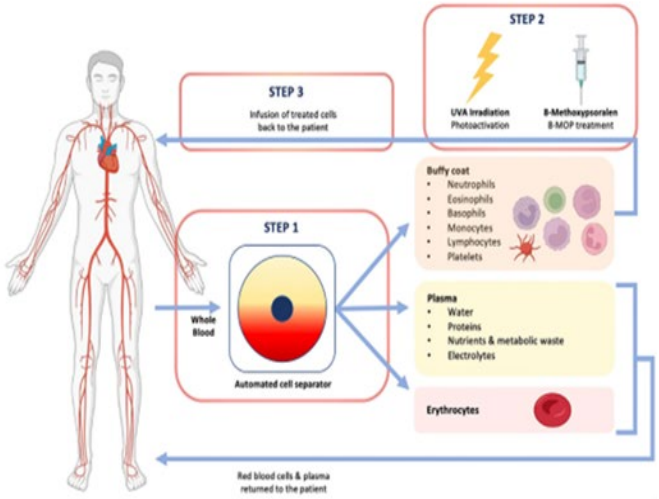


FIGURE 1
Overview of the ECP procedure.

Bojanic I Frontiers Immunol 2023

On-line
(one step)

MNC collection, irradiation and reinfusion on the same device

ECP technique

Off-line
(two steps)

-MNC collection by apheresis
-MNC manipulation and irradiation in a separate phase

No data on the optimal MNCs dose to infuse

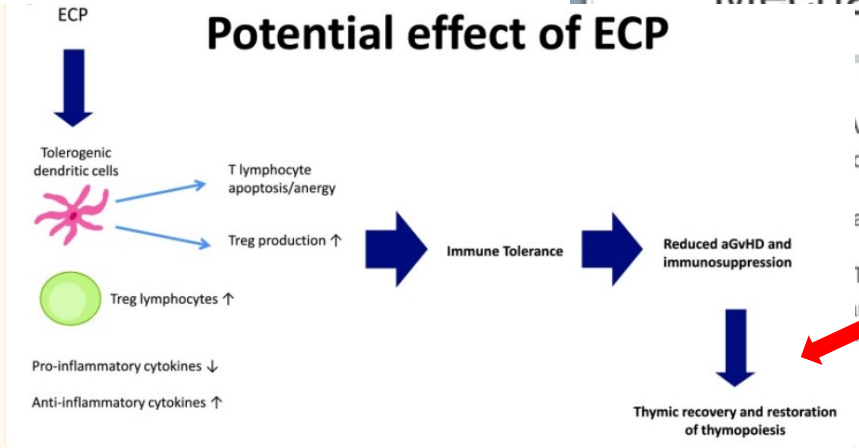
Immunomodulatory treatment with a high safety profile

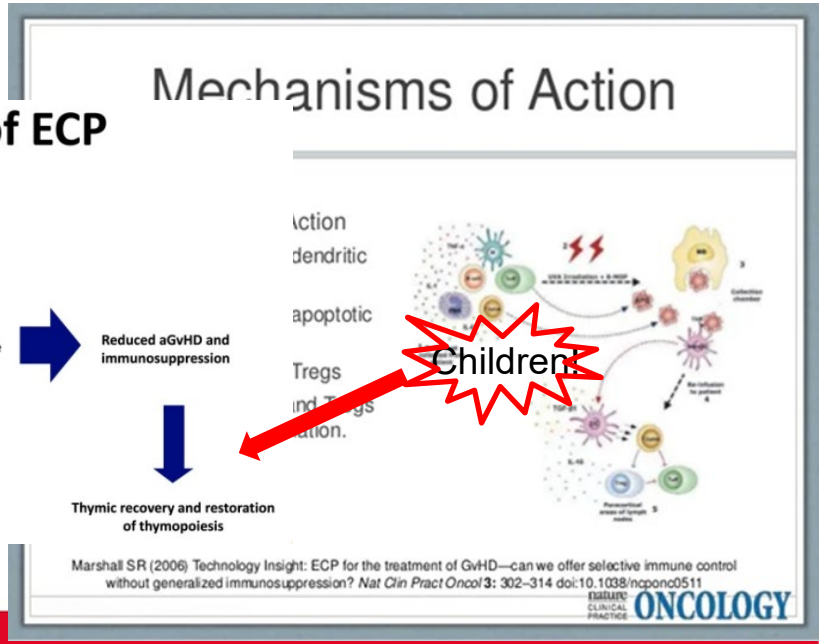
ECP promotes anti-inflammatory and tolerogenic responses

Patients respond nor illness

No global immunosu

In patients treated lo increased risk of mal





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Cochrane Library
Cochrane Database of Systematic Reviews

Buder K, Zirngibl M, Bapistella S, Meerpohl JJ, Strahm B, Bassler D, Weitz M.
Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents.
Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD009898.
DOI: 10.1002/14651858.CD009898.pub4.

Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents (Review)

Objectives

To evaluate the effectiveness and safety of ECP for the management of cGvHD in children and adolescents after haematopoietic stem cell transplantation.

Search methods

We searched the Cochrane Register
to 25 January 2021. We searched t
conference proceedings and nine cl

Selection criteria

We aimed to include randomised co
alone in children and adolescents w

Main results

We found no studies meeting the criteria for inclusion in this 2021 review update.

Authors' conclusions

We could not evaluate the efficacy of ECP in the treatment of cGvHD in children and adolescents after haematopoietic stem cell transplantation since the second review update again found no RCTs. Current recommendations are based on retrospective or observational studies only. Thus, ideally, ECP should be applied in the context of controlled trials only. However, performing RCTs in this population will be challenging due to the limited number of eligible participants, variable disease presentation and the lack of well-defined response criteria. International collaboration, multicentre trials and appropriate funding for such trials will be needed. If treatment decisions based on clinical data are made in favour of ECP, recipients should be carefully monitored for beneficial and harmful effects. In addition, efforts should be made to share this information with other clinicians, for example by setting up registries for children and adolescents treated with ECP.

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2023

ECP for GvHD in pediatric patients

Only case reports and case series in pediatric population

ORR: 70% aGvHD
60% cGvHD

Best response: skin involvement

Steroid sparing effect

Safe and effective, few side effects

Heterogeneity of treatment schedule

TABLE 1 Review of patients (indications for extracorporeal photopheresis [ECP], weight, age) blood prime criteria, venous access, and ECP schedule in published pediatric case series

Reference	Total no. patients	Total no. procedures	Indication	Mean or median weight in kg (range)	Mean or median age in yr (range)	Blood prime (Y/N)	Venous access	Schedule
Halle[5]	8	254	cGVHD ($n = 8$)	37 (18–49)	10 (5–15)	N	Tunnelized or double-lumen central catheter and/or peripheral access	2/wk for 2 wks, 1/wk or once every 2 wk for 3 mo
Salvaneschi[6]	23	NR	aGVHD (n=9), cGVHD (n=14)	35 (17–89)	10 (5–18)	N	Double-lumen central catheter ($n = 20$); peripheral access ($n = 3$)	aGVHD: 3/wk until improvement; cGVHD: 2 consecutive days at 2 wk interval for 3 mo
Messina[7]	77	NR	aGVHD (n=33), cGvHD (n=44)	aGVHD: 30 (10–85), cGVHD: 35 (15–68)	9 (0.3–21)	N	Double-lumen central catheter ($n = 50$); peripheral access ($n = 27$)	2 consecutive d/wk for 1 mo, once every wks for 2 mo, then monthly for 3 mo
Calore[8]	15	NR	aGVHD (n=15)	NR	10 (1–18)	Y	NR	2 consecutive d/wk for 1 mo, once every wks for 2 mo, then monthly for 3 mo
Kanold[9]	23	750	aGVHD (n=9), cGVHD (n=14)	aGVHD: 48 (13–68), cGVHD: 43 (13–80)	14 (4–18)	N	Tunnelized or double-lumen central catheter and/or peripheral access	3/wk for 3 wks, then tapering
Berger[10]	25	NR	aGVHD (n=15), cGVHD (n=10)	40 (17–72)	aGVHD: 11 (6–18), cGVHD: 12 (7–19)	N	NR	2 consecutive d/wk for 1 mo, once every wks for 2 mo, then monthly for 3 mo
Duzovali[11]	7	133	cGVHD (n=7)	32 (16–89)	10 (8–17)	Y, <40 kg	Double-lumen central catheter	3-5 d/wk, then tapering
Landolfo[12]	8	157	GVHD	19 (7–35)	NR	Y, <20 kg	Double-lumen central catheter with or without peripheral access	2 consecutive d/wk for 1 mo, 2 consecutive d/wk every 2 wk for 2 mo, 2 consecutive d/wk every mo for 6 mo
Linenberger[13]	7	287	GVHD	median NR (11–38)	median NR (3–14)	Y, <25 kg	NR	NR
Schneiderman[14]	11	334	cGVHD ($n = 9$), GVHD prophylaxis ($n = 2$)	29 (19–39)	NR	N	Single or double-lumen central catheter, peripheral access	Variable
Perotti[15]	73	2360	aGVHD ($n = 50$), cGVHD ($n = 23$)	aGVHD: 32 (SD 16), cGVHD: 39 (SD 17)	aGVHD: 10 (SD 5), cGVHD 12 (SD 4)	Y, <15 kg	Double-lumen central catheter (n=26); peripheral access (n=47)	2-3/wk until improvement, then tapering
Merlin[16]	12	NR	aGVHD ($n = 12$)	NR	11 (2–18)	NR	Tunnelized or double-lumen central catheter	3/wk for 3 wks, then tapering
González Vicent[17]	27	225	aGVHD (n=21), cGVHD (n=6)	30 (9–77)	10 (1–17)	Y, <15 kg	Double-lumen central catheter	aGVHD: 2 consecutive d/wk until improvement then tapering; cGVHD: 2 consecutive d at 2-wk intervals, then tapering
Rangarajan[18]	9	385	aGVHD ($n = 1$), cGVHD ($n = 8$)	49 (19–86)	14 (4–24)	Y, <35 kg	Double-lumen central catheter	2/wk until improvement, then tapering
Uygun[2]	12	194	aGVHD ($n = 6$), cGVHD ($n = 62$)	28 (7–68)	12 (2–17)	Y, <35 kg	Double-lumen central catheter (69%), single-lumen central catheter with peripheral access (10%), peripheral access only (21%)	2/wk for 2 mo, 2/wk every 2 wks for 2 mo, 2/wk every mo for at leat 1 yr
Kapadia[19]	10	440	aGVHD ($n = 5$), cGVHD ($n = 5$)	32 (22–65)	10 (8–27)	Y, <30 kg	Double-lumen central catheter, peripheral access, vortex port	2 consecutive sessions/wk, then tapering
Nelson[20]	30	NR	aGVHD ($n = 30$)	26 (7–138)	10 (1–33)	NR	NR	NR

Abbreviations: NR, not reported; cGVHD, chronic graft-versus-host disease; aGHVD, acute graft-versus-host disease; SD, standard deviation; kg, kilograms; yr, years; Y, yes; N, no; wk, weeks; d, days; mo, months.

De Simone et al, J Clin Apher 2017

ECP in pediatric patients: technical considerations

A child is not a small adult!

- Age 1 → 18 very different physiological and psycological considerations
- Different risk in AE related to ECP procedure (size <20Kg or >20 Kg)

CVC
Hemodynamic instability
Citrate toxicity
Anemia-thrombocytopenia

→ Possible procedure failure

Special considerations for ECP in pediatric setting

- Risk of hemodynamic instability (very low body weight children <15kg)
- Priming with irradiated and leukodepleted RBC
- Albumin for pts 20-25 kg?
- Suitable vascular access
- Higher risk of hypocalcemia → small children could be asymptomatic or not able to communicate symptoms
- Duration of apheresis procedure
- Psychological issues

between April 2014 and January 2018. Only few and mild side effects directly related to the ECP procedure were registered, even in patients with low body weight. The most frequent cause of shortened or canceled ECP treatment was difficulties with vascular accesses, which were more rarely seen using central venous catheters with larger lumens and made of stiffer material.

WINTHER-JØRGENSEN, Ped Transpl 2019

Sniecinski et al Transfusion and Apheresis Science 2017
Matic T et al J Clin Apher. 2019

Vascular access-CVC insertion

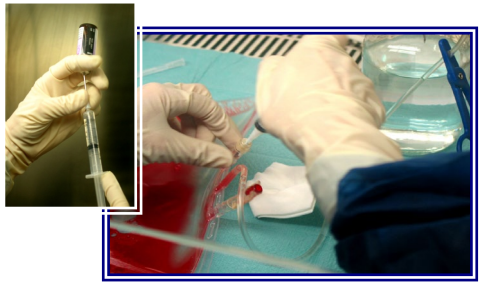
- No univocal consensus on CVC type
- Mild-moderate AE: pain,occlusion, bleeding, hematoma, infection (femoral)
- Potentially fatal AE: pneumothorax with hydrothorax (jugular or subclavian positioning)
- Essential for an optimal flow during collection (stable interface, short procedure time, small collection volume, lower risk of: citrate toxicity, fluid overload) **expecially in children<20 Kg**

Positioning must be performed by an expert physician, aware of apheresis technical needs

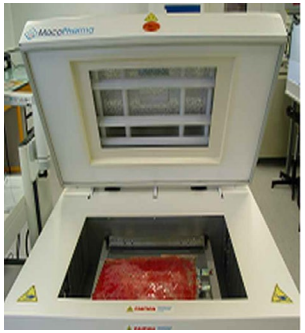
Pavia experience with GvHD using off-line technique

1) MNC collection by apheresis → 2) MNC manipulation → 3) MNC reinfusion

UV-A permeable bag



MNC irradiation



aGvHD treatment protocol

- 3 procedures/week (alternate days) until clinical improvement
- 2 procedures every week for 1-2 times (according to the clinical response)
- 2 procedures every 2 weeks (according to the clinical status and the immunosuppressive therapy tapering)

cGVHD treatment protocol

- 2 procedures every week for 2-3 times (according to the clinical response)
- 2 procedures every 2 weeks (according to the clinical status and the immunosuppressive therapy tapering) for 3 times
- 2 procedures monthly until ……..

ORIGINAL RESEARCH

Extracorpor
a longitud

Cesare Perotti

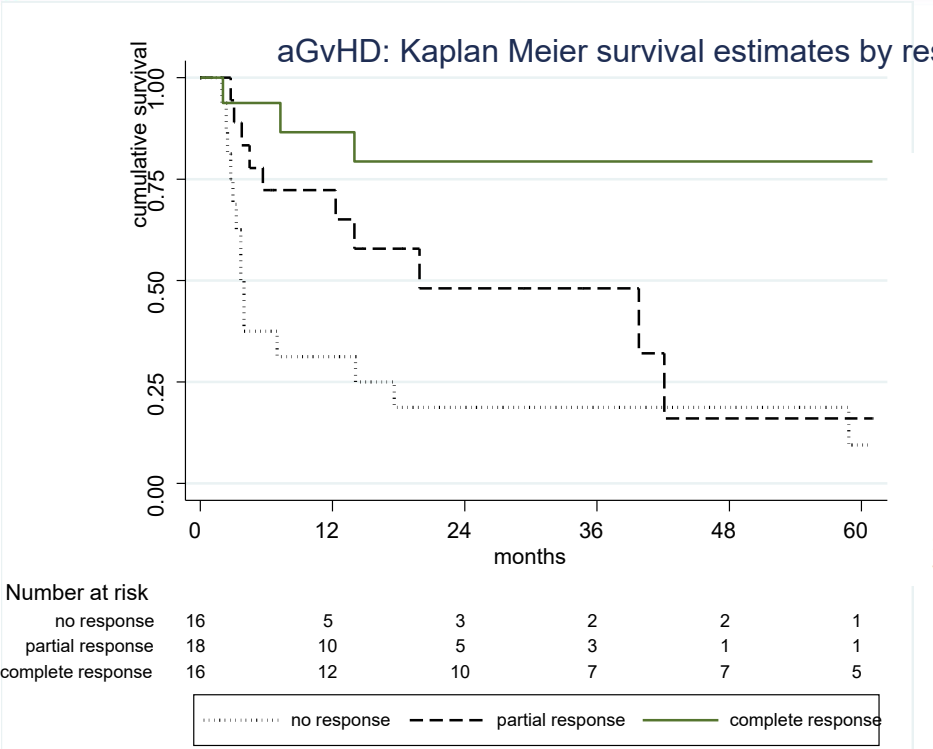
TABLE 2. Response to ECP and survival according to type of GVHD

Variable	Category	aGVHD (n = 50)	cGVHD (n = 23)
OR	CR (%)	16 (32.0)	5 (21.7)
	PR (%)	18 (36.0)	11 (47.8)
	NR (%)	16 (32.0)	7 (30.4)
Organ response	Skin (%)	39/47 (83.0)	22/23 (95.6)
CR and PR	Liver (%)	16/24 (66.7)	4/4 (100.0)
	Eyes (%)	2/4 (50.0)	2/4 (50.0)
	Lung (%)	0/2 (0.0)	2/3 (66.7)
	Join (%)	1/3 (33.3)	5/10 (50.0)
	Mucosae (%)	7/8 (87.5)	4/5 (80.0)
	Gut (%)	8/11 (72.7)	6/8 (75.0)
Steroid change	100% decrease (withdrawn) (%)	8 (16)	6 (26.1)
	99.9%-50% decrease (%)	18 (36)	4 (17.4)
	49.9%-0.1% decrease (%)	7 (14)	9 (39.1)
	Unchanged or increased (%)	17 (34)	4 (17.4)
Survival from transplantation	Deaths (%)	28 (56)	5 (21.7)
	Total follow-up	1268.2	1593.4
	Median follow-up (range)	14 (2-101.9)	59 (8.5-144.7)
	Estimated median survival time	19.9	131.6
	Survival at 1 year (%)	32 (64)	22 (95.7)
	Survival at 5 years (%)	23 (46)	19 (82.6)
	Deaths in responders (%)	13/34 (38.2)	2/16 (12.5)

50 pts with aGvHD
23 pts with cGvHD

aGvHD ORR: 68%
cGvHD ORR: 69.5%

Perotti C, Transfusion 2010



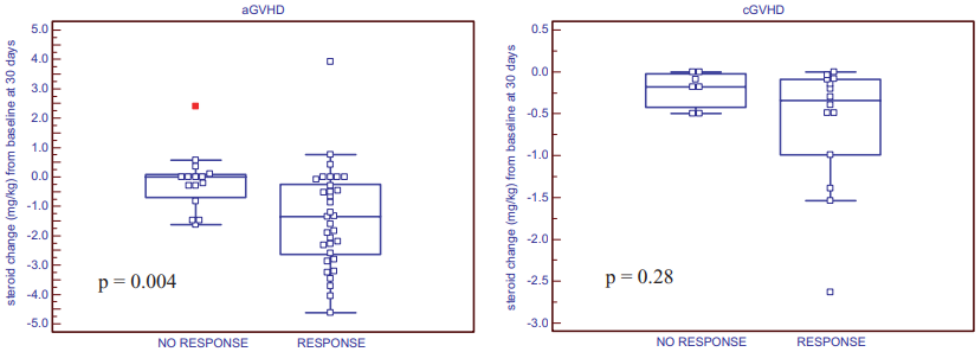


Fig. 1. Steroid change from baseline at 30 days in 50 aGVHD and 23 cGVHD pediatric patients. Central line = median; box = IQR; whiskers = 5th and 95th percentiles; filled squares = outliers.

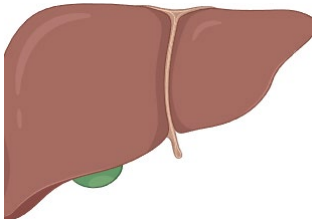
Steroid change

aGvHD

No association between grade of disease and response

+Steroid tapering of -1.3 mg/kg during the first 30 days in responders

GvHD with liver involvement



Start ECP as soon as possible
Intensive treatment (3x week) until improvement and steroid tapering

LETTERS TO THE EDITOR

Intensive extracorporeal photochemotherapy for severe acute hepatic graft-versus-host disease

Perotti C, Transfusion 2004

ECP side effects

Reported side effects

- ✓ Hypotension (range 0–27%)
- ✓ Catheter-related infections (range 0–42%),
- ✓ Abdominal pain (range 0–20%)

- ✓ Headache
- ✓ Chills
- ✓ Dizziness
- ✓ Hypocalcemia
- ✓ Vomit
- ✓ Diarrhea

Overall 3%

Pavia experience

2930 procedures

- Abdominal pain (hypocalcemia): 9 episodes
- Shivers: 14 episodes
- Headache: 25 episodes
- Fever post-MNC reinfusion : 13 episodes
- No hypotension or metabolic complications even in very low boy weight pts

Received: 28 April 2022 | Revised: 24 July 2022 | Accepted: 19 August 2022
DOI: 10.1002/jca.22012

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

Role of extracorporeal photopheresis in the management of children with graft-vs-host disease

Pedro Asensi Cantó[1] | Jaime Sanz Caballer[1] | Carolina Fuentes Socorro[2] | Pilar Solves Alcaína[1,3] | Pilar Lloret Madrid[1] | Jürgen Solís Ruíz[1] | Bárbara Torres Guerola[2] | Javier de la Rubia Comos[1,3,4] | José María Fernández Navarro[2] | Ines Gómez-Seguí[1,3]

Materials and Methods: Patients under 18 y of age with corticodependant or corticorefractory GVHD receiving ECP at our hospital were included in this retrospective study. ECP was performed with an in-line system (CellExTherakos) in 2013-2014 and with an off-line system (Spectra Optia) from 2015 onwards. Cumulative incidence curves were obtained to compare ECP efficacy among patients grouped by different baseline, apheresis, and disease characteristics. Significant variables on univariate analysis (Gray's test) were pooled into a multivariate analysis (Fine-Gray proportional hazard regression for competing events).

Results: A total of 701 ECP sessions were performed on 33 patients between October 2013 and December 2021. In total, 97% of the sessions could be executed. In 8% of the sessions an incident was detected, most of them mild and related to catheter dysfunction. With a median follow-up for alive patients of 33.6 mo (range, 8-95), the composite partial and complete response cumulative incidence was 70% (95% confidence interval, 51%-82%) and the median time to maximal response was 2.8 mo (range, 0.25-9.8). Significantly lower response ratios were found in patients with hepatic, gastrointestinal, acute, or severe GVHD. The only variable that influenced response on multivariate analysis was GVHD severity.

Patients' characteristics	n = 33 Median (range)
cGVHD	
Cutaneous	8 (89)
Oral	4 (45)
Pulmonary	2 (22)
Ocular	1 (11)
Musculoskeletal	1 (11)
Organ involvement	
aGVHD	
Cutaneous	21 (88)
Gastrointestinal	9 (39)
Hepatic	3 (11)

Response to ECP is fast (median 44 days for CR and 21 days for PR)
Low rate of exacerbations
Benefit in intensification in aGvHD (2 sessions/week)

ORR: 70%
Overall steroid reduction (>50%): 57%,
Steroid suspension:39% (43% aGvHD, 50% cGvHD, 20% a+cGvHD)

aGVHD: 29 pts 52% CR, 14% PR, 34% NR.
Best response skin
Lower in liver, gut and lower grade of aGvHD

cGVHD: 4 pts, 20% CR (skin), 30% PR, 50% NR

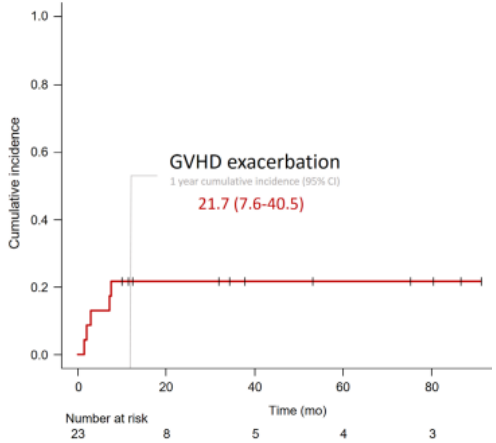


FIGURE 3 Cumulative incidence of graft-vs-host disease (GVHD) exacerbation for responding patients.

Asensi-Cantò et al, J Clin Apher. 2022

Received: 17 June 2020 | Revised: 26 June 2020 | Accepted: 28 June 2020
DOI: 10.1002/jha2.58

eJHaem

SHORT REPORT

A survey of extracorporeal photopheresis treatment in pediatric patients in the United Kingdom

Aisling M. Flinn[1] | Sheba Macheka[1] | Mary Slatter[1] |
Brenda Gibson[2] | Sarah Lawson[3] | Anna Tailby[3] | Giova
Helen New[5] | Beki James[6] | Arun Alfred[7] | Julia Scarisb

Also very low bw pts deserve ECP
Early is better

98 pts treated with ECP from 2010 to 2017 for SR, SD, SI GvHD

72/98 pts with aGvHD: 44.1% CR, 18.1 PR

26/98 pts with cGvHD: 40% CR, 13,3% PR

4 | DISCUSSION

This survey provides important insight into delivery of pediatric ECP in the United Kingdom. Most patients received ECP with minimal side effects, reinforcing the evidence that it is safe and well tolerated in

were
e vul-
P has
s with
in the
disease course, important as early ECP initiation is associated with better clinical outcomes [8]. The number and wide range of differ-

of death (unknown in 70%). 30 patients in this cohort died, including 50% of patients ≤10 kg, the majority who were on significant immune suppression, again highlighting the vulnerability of this population and the need to find ways to improve their management and clinical outcomes. Identifying gaps in our knowledge regarding management of this patient cohort supports the need to include ECP treatment data to national transplant databases. There is a lack of data to inform clini-

ECP in children needs:

- ✓ Hospitals offering all facilities
- ✓ Trained and motivated personnel
- ✓ Intensive cooperation with Pediatricians
- ✓ Optimal organization
- ✓ Special psychological approach in apheresis ward

Received: 29 November 2022 | Revised: 25 January 2023 | Accepted: 27 January 2023
DOI: 10.1002/jca.22043

Guidelines on the Use of Therapeutic A
Practice – Evidence-Based Approach fr
Committee of the American Society for
The Ninth Special Issue

GRAFT-VERSUS-HOST DISEASE

Incidence: after allogeneic HSCT, grade II to IV aGVHD in up to 60%; cGVHD in up to 70%

Indication	Procedure		Category	Grade
Acute/Chronic	ECP		II	1B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Acute	1 (81)	6 (296)	NA	NA
Chronic	2 (148)	8 (228)	NA	NA

HSCT = hematopoietic stem cell transplant; aGVHD = acute GVHD; cGVHD = chronic GVHD.

Graft-versus-host disease	Acute	ECP	II	1B
	Chronic	ECP	II	1B

II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation

Management of SR acute and chronic GvHD

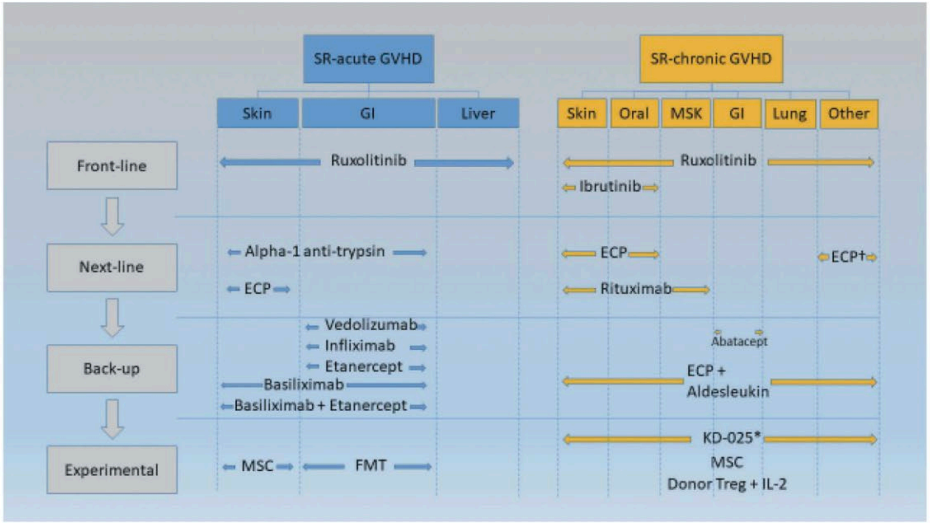


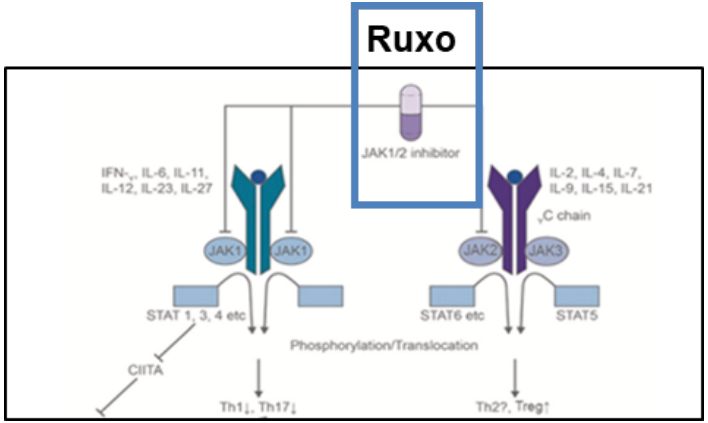
Figure 1. Suggested approach to the management of steroid-refractory (SR) acute and chronic GVHD.

Arrows represent the availability of evidence for efficacy of a therapy for a particular organ manifestation of SR-acute or SR-chronic GVHD. The order of therapy selection reflects the evidence outlined in the current review but does not imply a strict order. For example, there is no strict guidance to choose Vedolizumab before Infliximab for gut SR-acute GVHD, but one may choose to use alpha-1-antitrypsin before Vedolizumab for this condition. The absence of arrows for a particular experimental therapy suggests ongoing study without clear evidence of organ-specific efficacy. †ECP has been suggested to have efficacy in ocular and hepatic chronic GVHD as well. *KD-025 is still considered an experimental therapy at the time of this publication, but may soon receive FDA approval for the treatment of SR-chronic GVHD that has been refractory to at least two lines of therapy. Abbreviations: ECP, extracorporeal photopheresis, MSC, mesenchymal stem cells, FMT, fecal-microbiota transfer, Treg, regulatory T-cells, IL-2, interleukin-2.

Ruxolitinib in SR GvHD

In randomized trials (Ruxo vs BAT)
Effective in aGVHD and cGvHD
Higher response rates
Limitations of the studies: subgroup analyses (different second line treatments)

Durability of response in SR aGvHD
Response in eye, liver and lung manifestations



Received: 1 December 2019 | Revised: 18 January 2020 | Accepted: 6 February 2020
DOI: 10.1002/pbc.28233
Pediatric Blood & Cancer
TRANSPLANTATION: RESEARCH ARTICLE

Ruxolitinib in children with steroid-refractory acute graft-versus-host disease: A retrospective multicenter study of the pediatric group of SFGM-TC

Louise Laisne[1] | Benedicte Neven[2] | Jean-Hugues Dalle[3] | Claire Galambrun[4] | Maxime Esvan[5] | Cecile Renard[6] | Fanny Rialland[7] | Anne Sirvent[8] | Virginie Gandemer[1] | on behalf of the Pediatric Group of SFGM-TC[1]

- 29 pts
- CR 65.5 %
- ORR 72.4%

TABLE 3 Univariate analysis for the association of baseline characteristics and response to ruxolitinib

	CR/PR	Failure	OR [IC 95%]	P
Number of patients				
Age	21	8		0.2453
< 6 years	13	3	1	
> 6 years	8	5	0.37 [0.07-1.98]	
Weight				0.9759
< 15 kg	7	3	1	
15-30 kg	11	4	1.18 [0.20-6.93]	
> 30 kg	3	1	1.29 [0.09-17.95]	
Isolated skin aGVHD				0.5091
No	16	7	1	
Yes	5	1	2.19 [0.21-22.34]	
GI aGVHD				0.6433
No	6	3	1	
Yes	15	5	1.50 [0.27-8.34]	

STUDY | **REACH5: the safety and efficacy of ruxolitinib in paediatric patients with cGvHD**

Population: N = 45

Primary endpoint: Overall response rate at Cycle 7, Day 1.

Eligibility: Treatment naïve, SR-cGvHD, undergone a successful alloSCT.

TRIAL DESIGN

Group 1	Group 2	Group 3
Aged between **≥12** and **<18 years**	Aged between **≥6** and **<12 years**	Aged between **≥2** and **<6 years**
Ruxolitinib	**Ruxolitinib**	**Ruxolitinib**
10 mg BID	**5 mg BID**	**4 mg/m² BID**

All patients received corticosteroids

Up to 156 weeks (39 cycles of 28 days)

Data analyzed at 1 year of treatment (or discontinuation if earlier)

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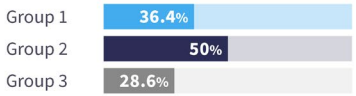
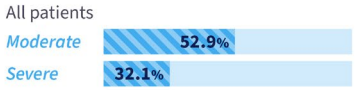
EFFICACY

ORR at C7D1



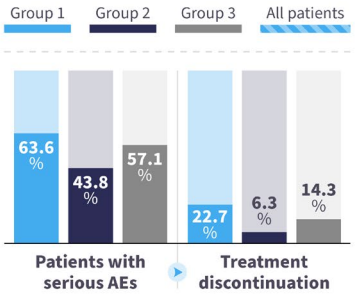


BOR at C7D1

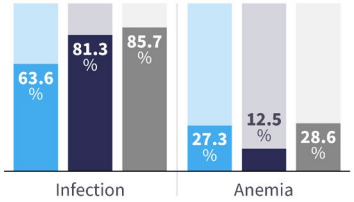
All patients (12 months)

Tapered off corticosteroids by C7D1

SAFETY



Most common AE (any grade)



All patients

Across all age groups, ruxolitinib treatment led to high rates of overall response at C7D1 in pediatric patients with cGvHD.

Abbreviations: AE, adverse event; alloSCT, allogeneic stem cell transplant; BID, twice daily; BOR, best overall response; cGvHD, chronic graft-versus-host disease; C7D1, Cycle 7, Day 1; IV, intravenous; ORR, overall response rate; PFS, progression-free survival; SR, steroid refractory.

Locatelli F. Ruxolitinib in pediatric patients with treatment-naïve or steroid refractory chronic graft versus host disease: primary findings from the phase II REACH5 study. Oral abstract #S245. European Hematology Association 2023 Hybrid Congress; Jun 10, 2023; Frankfurt, DE

Ruxolitinib: emerging adverse events

Anemia (65%)
Thrombocytopenia (62%)
Neutropenia (48%)
Infections
CMV reactivation (13%)
Bacteriemia (10%)
Sepsis (13%)

Martini DJ, Oncologist 2022
Zeiser ,New Engl J Med 2020

Inhibition of proinflammatory signals and modulation of cell populations

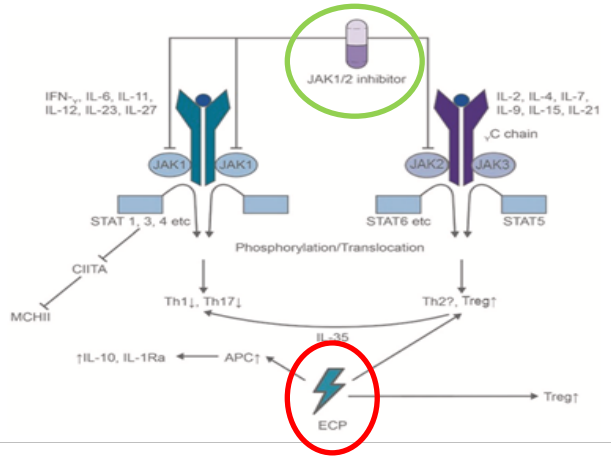


Fig. 1 Complementary mechanisms of action of extracorporeal photopheresis plus ruxolitinib.

Ruxo+ECP ?

Goals:

Act on immunologic mechanisms promoting GvHD

Suppress T cell expansion

Promote Treg proliferation

Preserve GvL effect

ECP+RUXOLITINIB: better response?

Bone Marrow Transplantation (2021) 56:909–916
https://doi.org/10.1038/s41409-020-01122-8

ARTICLE

Ruxolitinib–ECP combination treatment for refractory severe chronic graft-versus-host disease

Kristina Maas-Bauer[1] · Chrissoula Kiote-Schmidt[1] · Hartmut Bertz[1] · Petya Apostolova[1] · Ralph Wäsch[1] · Gabriele Ihorst[2] · Jürgen Finke[1] · Robert Zeiser[1]

Retrospective study

23 adult pts SR cGvHD under Ruxo-ECP

- ECP schedule: 2 procedures /2-4 weeks (median treatm 6 mo)
- CR+PR: 74% (CR:9%, PR: 65%)
- Gut and skin cGVHD (54%, 44%) responded better than liver, eye, and lung (21, 20, and 13%)
- 76% responders steroid tapering
- 24-months survival: 75% (CI: 56-94.1)
- Reduction of serum soluble interleukin-2 receptor in responders

Bone Marrow Transplantation (2020) 55:2286–2293
https://doi.org/10.1038/s41409-020-0952-z

EBMT

ARTICLE

Ruxolitinib plus extracorporeal photopheresis (ECP) for steroid refractory acute graft-versus-host disease of lower GI-tract after allogeneic stem cell transplantation leads to increased regulatory T cell level

Franziska Modemann[1,2] · Francis Ayuk[1] · Christine Wolschke[1] · Maximilian Christopeit[1] · Dietlinde Janson[1] · Ute-Marie von Pein[1] · Nicolaus Kröger[1]

Retrospective study

Ruxo+ ECP in 18 adult patients with severe steroid refractory aGVHD of lower GI-tract.

RESULTS

- ✓ ORR: 55% (CR:44%, PR :11%)
- ✓ Rapid steroid tapering
- ✓ Moderate cytopenia in 3/18 pts
- ✓ 2yrs OS: 56% (70% in CR or PR)
- ✓ Increased Tregs

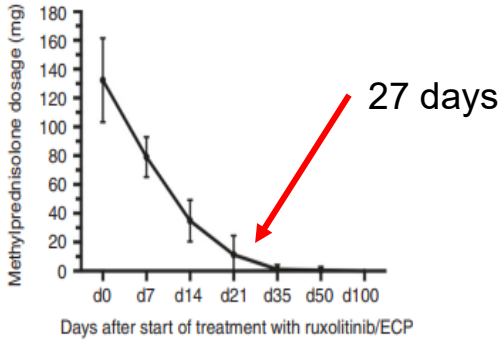


Fig. 3 Reduction of methylprednisolon in mg after start of treatment with ruxolitinib/ECP. Reduction of steroids under the treatment with ruxolitinib/ECP.

Ruxo+ECP: preliminary results

Promising second line approach in SR GvHD: synergistic effect in reducing pro-inflammatory signals and modulate different cell populations

Increase Tregs (mouse model)

Good response rate (≈ 70%) and tolerable toxicity profile

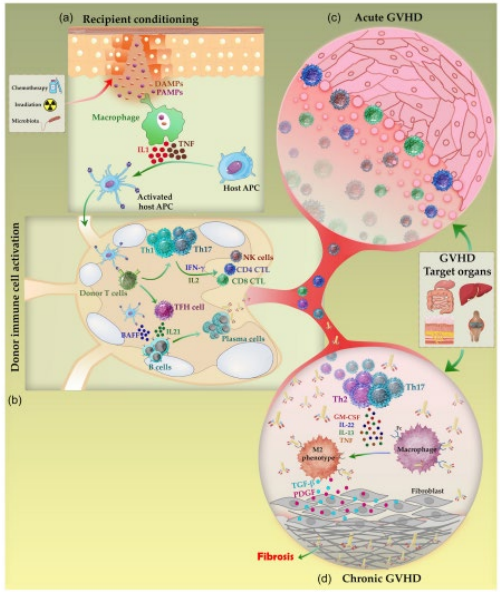
Responders were able to taper steroids rapidly

Need for biomarkers (easy and quick to perform) to predict response to ECP treatment

Goals:

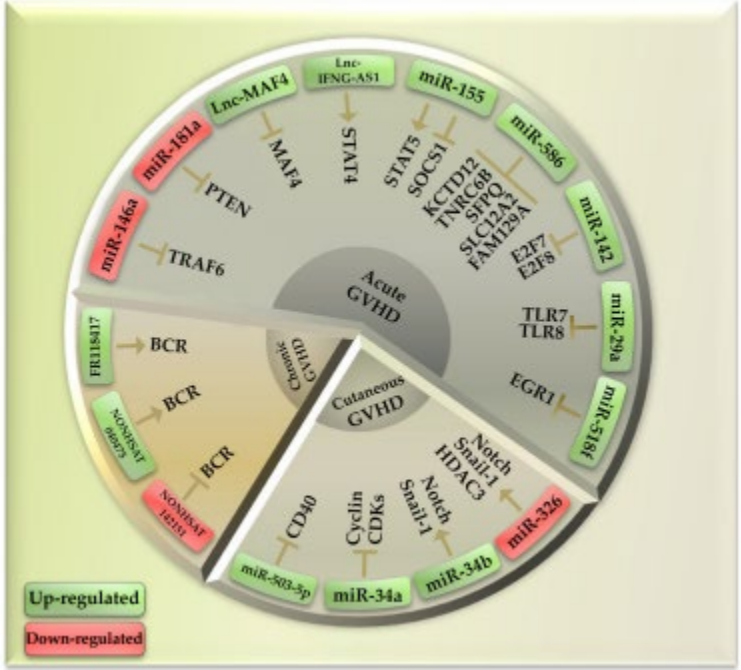
- Personalized treatment for a better cGvHD clinical management
- Maximise response ⇨ organ involvement
- Reduction of costs and patient discomfort

MiRNA: non coding RNAs with critical regulatory functions

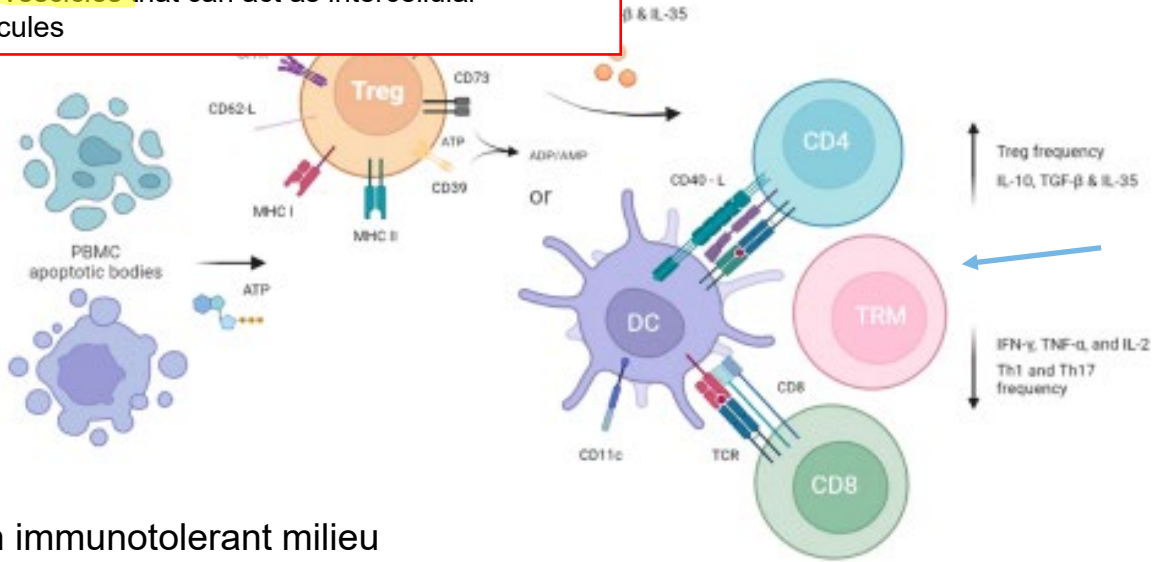


Circulating miRNAs have the potency of serving as novel and noninvasive biomarkers for different diseases, including autoimmune disorders and inflammatory diseases (aberrantly expressed in many diseases, presents in biofluids, stable).

Considering the variety of their roles, miRNAs are <u>potential targets for the modulation of allogeneic immune responses in GVHD</u>



T-reg enforce peripheral tolerance and suppress Th1 response via miRNA/ extracellular vescicles that can act as intercellular communication molecules



ECP may favour an immunotolerant milieu

FIGURE 2
Hypothesised mechanism of ECP and tolerogenic immune cells immunosuppressive effects. The effect of ECP is first seen in the blood compartment where a portion of PBMCs go into apoptosis. Apoptotic bodies released by the PBMCs circulate and interact with Tregs as well as tissue-resident cells such as DCs, leading to tolerisation. Immunosuppression is achieved through cytokine excretion and cell-to-cell contact with mediators of GvHD such as CD4+ T helper cells, CD8+ T cells, and Tissue Resident Memory T cells.

Remarks

- ECP is feasible, safe and effective also in very low body weight children (<15kg)
- Consolidated in second line treatment of SR aGVHD and chronic GvHD
- ECP is a sparing steroid treatment and improves QoL
- ECP often utilized late in the disease course (early is better!)
- Data limited mainly to small non randomized studies (heterogenous treatment)
- Vascular access: may be a limitation to ECP therapy
- Ruxolitinib+ECP: may be a new treatment option for SR GvHD
- ECP intensive course in case of severe neutropenia or anemia related to Ruxolitinib