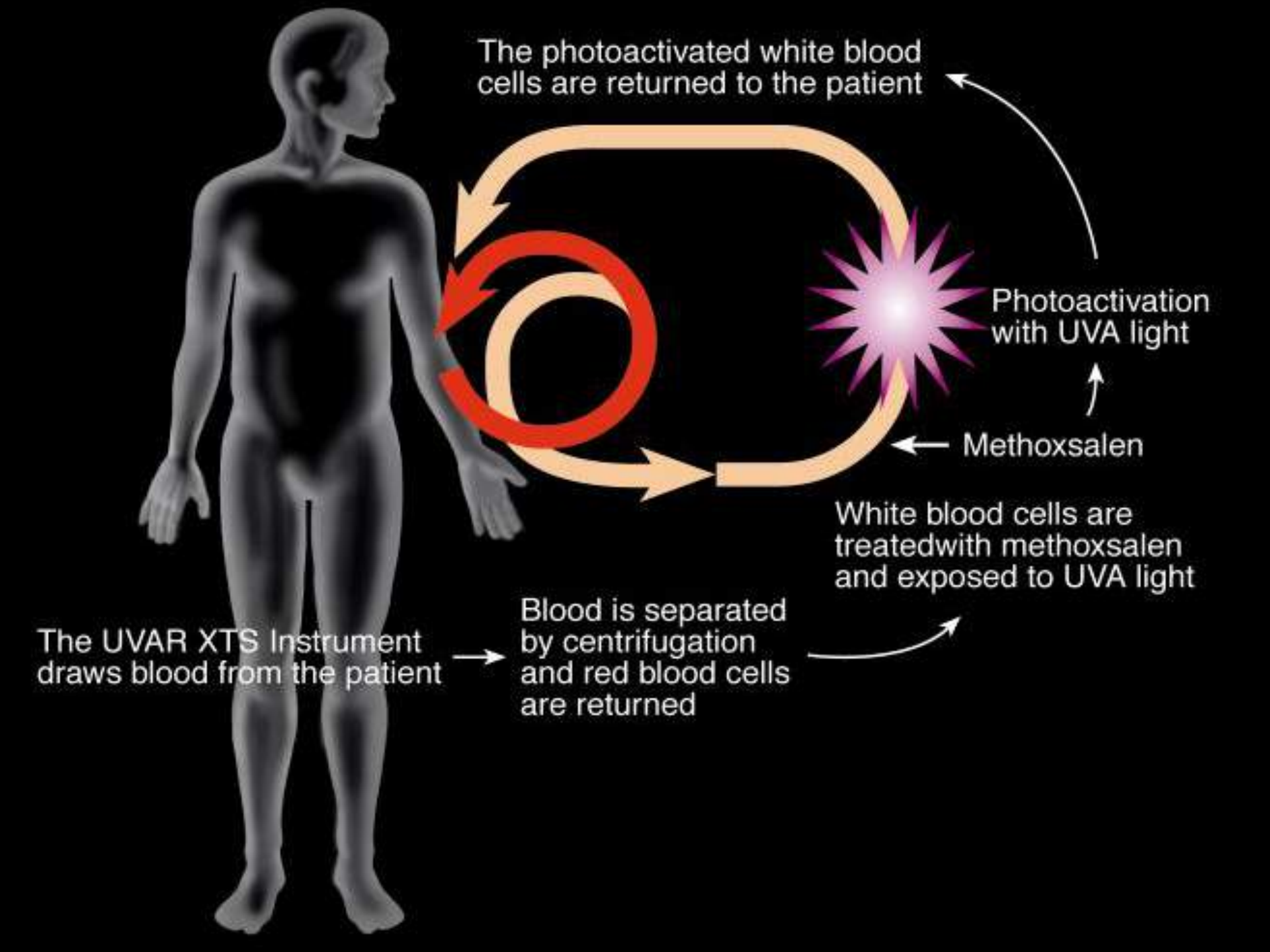
Φωταφαίρεση
(Extracorporeal Photopheresis-ECP)

Ελένη Γαβριηλάκη
Αιματολογική Κλινική – Μονάδα Μεταμόσχευσης
Νοσοκομείο «Γ. Παπανικολάου», Θεσσαλονίκη

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ


The photoactivated white blood cells are returned to the patient
Photoactivation with UVA light
Methoxsalen
White blood cells are treatedwith methoxsalen and exposed to UVA light
Blood is separated by centrifugation and red blood cells are returned
The UVAR XTS Instrument draws blood from the patient

Technical comparison of four different extracorporeal photopheresis systems

Andreas Brosig,[1†] Viola Hähnel,[1†] Evelyn Orsó,[1] Daniel Wolff,[2] Ernst Holler,[2] and Norbert Ahrens[1]

Offline

Online

TABLE 1. Patient characteristics*

Characteristics	Amicus	Cobe Spectra	Spectra Optia	Therakos	Overall
Number of patients	12	22	7	10	31
Male/female (% males)	75	55	43	50	52
Age† (years)	53 (17-69)	51 (17-69)	48 (17-59)	64 (19-76)	52 (17-76)
Total blood volume† (L)	5.2 (3.8-6.6)	5.0 (3.1-6.6)	4.6 (3.7-5.7)	4.7 (3.5-7.2)	4.9 (3.1-7.2)
Diagnoses					
Acute GVHD	2	7	3	4	16
Chronic GVHD	8	25	5	10	48
Sézary's disease	3	9	2		14
Atopy	2	4		3	9
Scleroderma		2		4	6
Collagenosis		1	1		2
Crohn's disease	1	1			2
Bronchiolitis obliterans after lung transplantation		5	1	4	10
Treatments	16	54	12	25	107
Included treatments per patient	1 (1-2)	2 (1-6)	2 (1-3)	2 (1-6)	3 (1-8)
Full blood count before apheresis					
WBCs ($\times 10^9$/L)	6.0 (2.4-12.2)	6.4 (2.1-13.0)	4.1 (2.8-10.0)	5.8 (3.0-14.3)	5.8 (2.1-14.3)
Hb† (g/dL)	12.4 (9.0-15.1)	12.1 (7.7-15.3)	12.1 (9.4-14.3)	10.4 (8.4-15.0)	12.0 (7.7-15.3)
Hct† (%)	36 (27-44)	36 (25-44)	36 (29-40)	33 (26-43)	36 (25-44)
Thrombocytes† ($\times 10^9$/L)	216 (76-451)	218 (26-574)	181 (76-327)	312 (33-693)	232 (26-693)
Neutrophils (%)	71 (22-88)	67 (25-91)	66 (47-87)	70 (52-93)	68 (22-93)
Lymphocytes (%)	16 (2-51)	17 (2-47)	16 (2-32)	15 (5-32)	16 (2-51)
Monocytes (%)	11 (4-24)	11 (1-23)	13 (10-23)	10 (1-27)	11 (1-27)

TABLE 2. ECP procedure data*

Procedure parameter	Amicus	Cobe Spectra	Spectra Optia	Therakos	Overall
Procedure time†‡ (min)	166 (120-245)	160 (123-195)	140 (120-193)	192 (155-275)	164 (120-275)
Volume of apheresate† (mL)	200 (183-208)	200 (150-233)	197 (195-200)	268 (207-342)	200 (150-342)
Processed volume† (L)	7.9 (7.8-8.0)	8.3 (2.8-11.7)	7.5 (6.9-7.6)	NA	7.9 (2.8-11.7)
Anticoagulation rate†	1:11.4 (11.1-12.3)	1:10.3 (7.8-11.2)	1:11.0 (9.6-11.0)	NA	1: 10.9 (7.8-12.3)
WBC CE (%)	16 (6-44)	12 (1-47)	21 (4-38)	NA	14 (1-47)
MNC CE (%)	60 (41-86)	50 (10-88)	60 (41-81)	NA	54 (10-88)
WBC throughput (mL/min)	7 (2-23)	7 (0.7-26)	11 (2-19)	3 (0.07-5)	7 (0.07-26)
MNC throughput (mL/min)	31 (19-38)	28 (2-46)	33 (16-45)	6 (0.2-9)	27 (0.2-46)

- Συγκρίσιμα κυτταρικά προϊόντα
- Περισσότερα μονοκύτταρα / χαμηλότερος αιματοκρίτης με online σύστημα

Σύστημα φωταφαίρεσης


PHOTOACTIVATE
UVA ON
MINUTES
10:25
REMAINING
TREATMENT STATUS
TREATMENT VOLUME 284 ml
SALINE VOLUME 194 ml
A/C VOLUME 292 ml
ELAPSED TIME (HH:MM) 02:38
FLOW RATE 0 ml/min
SYSTEM STATUS
REMAINING LAMP LIFE 76.2 hrs
INSTRUMENT S/N 30386
INSTRUMENT HOURS 3173.9 hrs
VER. 3.03/2.01/1.13/1.11
TREATMENT SETTINGS
COLLECT RATE LIMIT 75 ml/min
COLLECT PRESSURE -50 mmHg
RETURN RATE LIMIT 100 ml/min
RETURN PRESSURE 200 mmHg
REINFUSION RATE LIMIT 100 ml/min
CYCLES 6
SALINE BOLUS 100 ml
A/C RATIO 12:1
STOP
THERAKOS
Johnson & Johnson company

Προφυλάξεις

- Παρακολούθηση του αριθμού των αιμοπεταλίων πριν και μετά τη χορήγηση ηπαρίνης
- Ο προσωρινός εξωσωματικός όγκος δεν πρέπει να υπερβαίνει το 15% του εκτιμώμενου συνολικού όγκου αίματος του ασθενή
- Αντενδείκνυται σε ασθενείς που έχουν υποβληθεί σε σπληνεκτομή ή παρουσιάζουν ανωμαλίες πήξης, ή έχουν λευκά αιμοσφαίρια >25.000/mm^3
- Απαιτείται αντισύλληψη
- **Προστασία από το φως** έως και 24h μετά τη θεραπεία

Ανεπιθύμητες ενέργειες

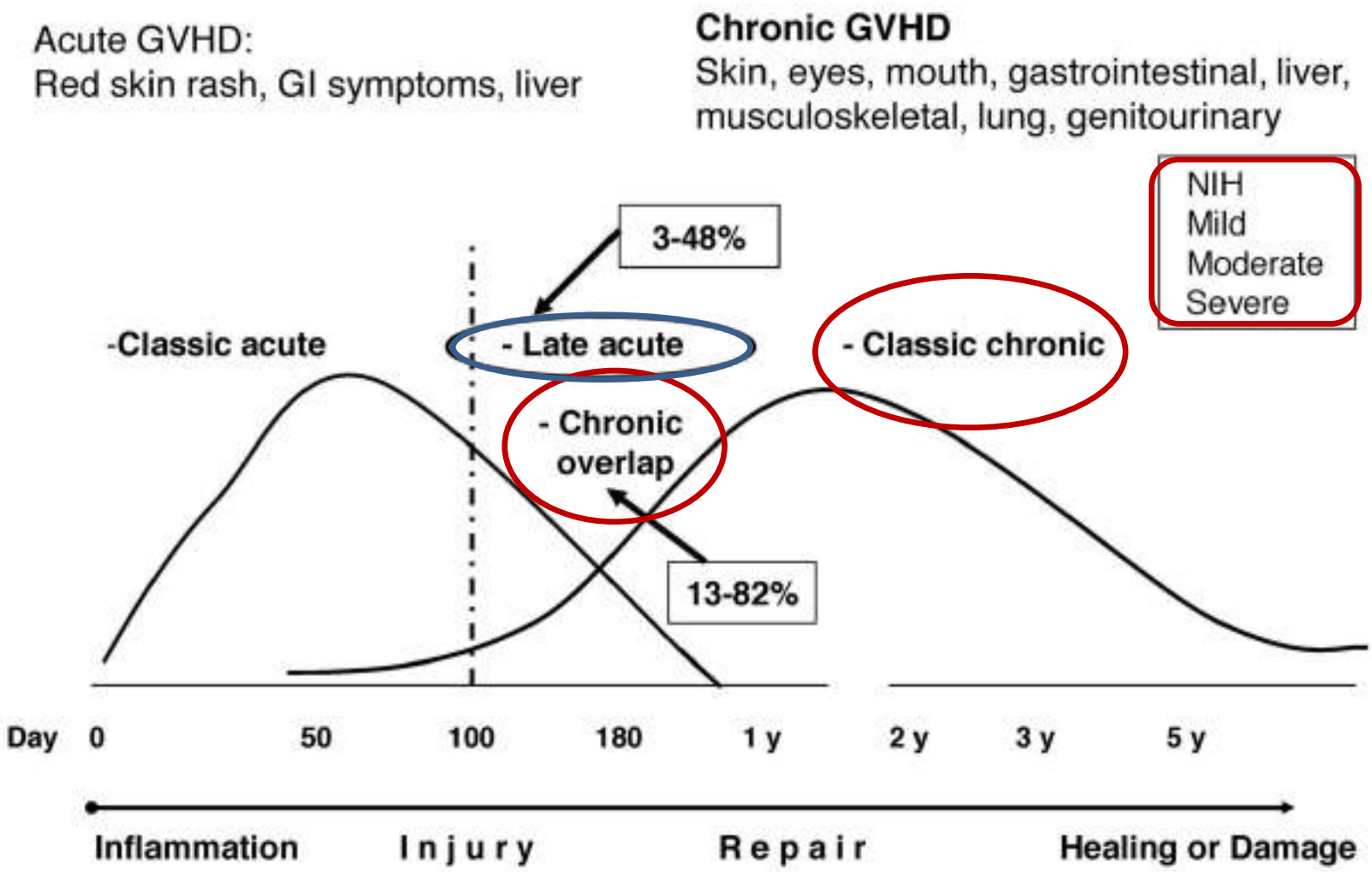
- Υπόταση κατά τη διάρκεια της θεραπείας
- Παροδικές πυρετικές αντιδράσεις
- Προσωρινή αύξηση του ερυθροδέρματος
- Αναιμία
- Πόνος και φλεγμονή στο σημείο φλεβοκέντησης

Αιματολογικά νοσήματα

Νόσος μοσχεύματος κατά ξενιστή

Δερματικό Τ λέμφωμα

GVHD classification after the NIH consensus conference.

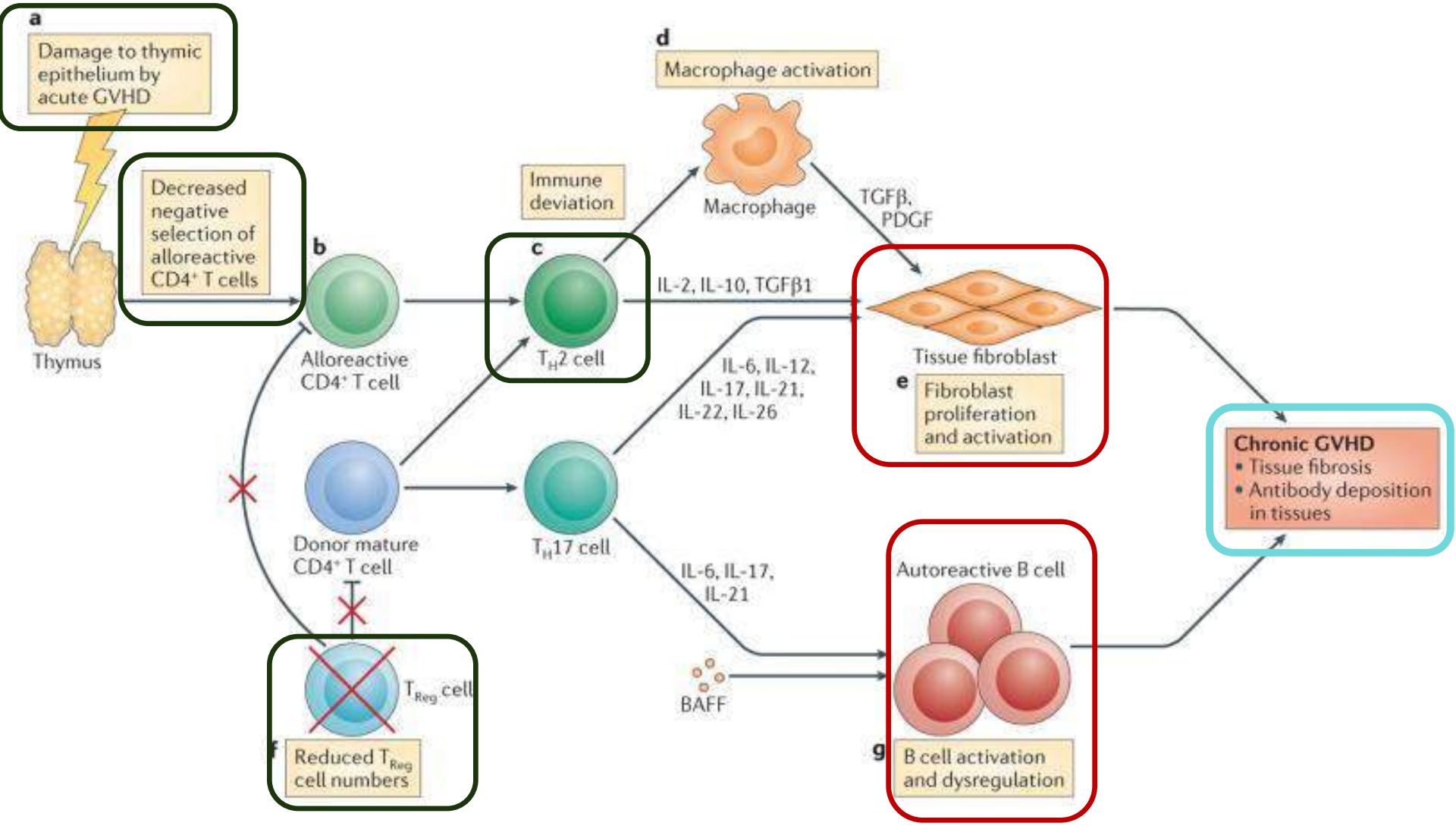


Pavletic S Z , and Fowler D H Hematology 2012;2012:251-264

Nat Rev Immunol. 2012 May 11;12(6):443-58.

Advances in graft-versus-host disease biology and therapy.

Blazar BR, Murphy WJ, Abedi M.



NIH Consensus for Scoring of cGVHD

Organ scoring of chronic GvHD - Tick relevant box for each organ and give result where indicated

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus

Other sites:

Mouth

Eyes

Gastrointestinal tract

Liver

Lungs

Joints and fascia

Female genital tract

Hematology Am Soc Hematol Educ Program. 2012;2012:251-64.

Are we making progress in GVHD prophylaxis and treatment?

Pavletic SZ, Fowler DH.

Μέση διάρκεια cGVHD: 2-3 χρόνια.

≈ 85% των ασθενών που επιβιώνουν >5 χρόνια διακόπτουν την ανοσοκαταστολή

Στόχος της θεραπείας της cGVHD:

- Καταστολή των ανοσολογικών μηχανισμών, ανακούφιση συμπτωμάτων, πρόληψη της προόδου νόσου σε μη αναστρέψιμες βλάβες οργάνων.
- Επίτευξη ανοσολογικής ανοχής.

Ενδείξεις συστηματικής θεραπείας

μέσης και σοβαρής βαρύτητας cGVHD

- **Συμμετοχή ≥ 3 οργάνων**

ή

- **≥ 2 οργάνων με NIH score ≥ 2 σε οποιοδήποτε όργανο**

ή

- **Συμμετοχή πνευμονικής νόσου**

cGvHD
1ης γραμμής θεραπεία

Κορτικοστεροειδή ± CNI

cGvHD
2ης γραμμής θεραπεία

Κορτικο-άντοχη και κορτικο-εξαρτώμενη cGvHD

(1) progression on prednisone at 1 mg/kg/day for 2 weeks,

(2) stable disease on > 0.5 mg/kg/day of prednisone for 4-8 weeks,

(3) inability to taper prednisone below 0.5 mg/kg/ day.

Κορτικο-άντοχη και κορτικο-εξαρτώμενη cGvHD

- Δεν υπάρχει standard θεραπεία 2ης γραμμής.
- Παρά το ότι 50% των ασθενών απαντούν στην αρχική θεραπεία, η πρόγνωση των ασθενών με ανθεκτική νόσο στη θεραπεία 1ης γραμμής παραμένει δυσμενής.
- Τα δεδομένα στην κορτικοάντοχη cGVHD περιορίζονται σχεδόν αποκλειστικά σε αναδρομικές ή μελέτες φάσης ΙΙ.

  (Response 25%-80% και 1-3ετή επιβίωση περίπου 70%)

  Η απάντηση είναι συχνά μερική και πρόσκαιρη.
- Η αναγνώριση της κατάλληλης θεραπείας ή συνδυασμού παραγόντων για έναν ασθενή στηρίζεται ακόμα στο «trial-and error».

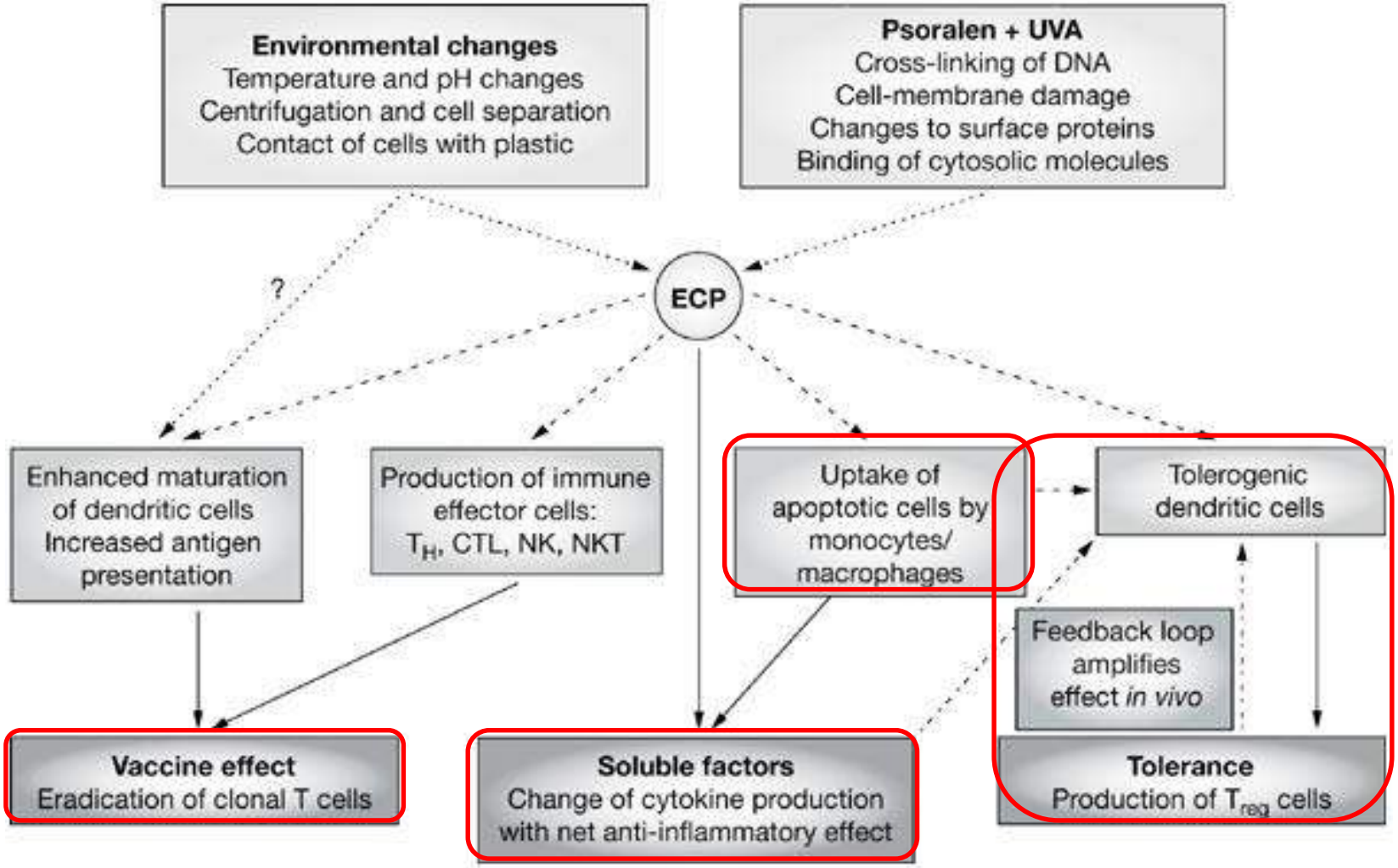
ECP στην κορτικο-άντοχη και κορτικο-εξαρτώμενη cGvHD

- 1996: πρώτα αποτελέσματα εφαρμογής της ECP σε cGvHD *(Rossetti et al)*
- Απάντηση δέρμα (72%), στοματικό βλεννογόνο (74%) και ήπαρ (63%)
- ECP: ανοσο-τροποποιητική, καταστολή της GvHD χωρίς αύξηση λοιμώξεων και υποτροπής της κακοήθους νόσου, δυνατότητα ελάττωσης και διακοπής της κορτιζόνης και ανοσοκαταστολης.

  Γενικά καλά ανεκτή με αυξημένη μακρά επιβίωση σε ασθενείς που ανταποκρίνονται.
- Μειονέκτημα: υψηλό κόστος θεραπείας ?

Scott R Marshall . ***Technology Insight: ECP for the treatment of GvHD—can we offer selective immune control without generalized immunosuppression?*** *Nature Clinical Practice Oncology (2006)* ***3****, 302-314*

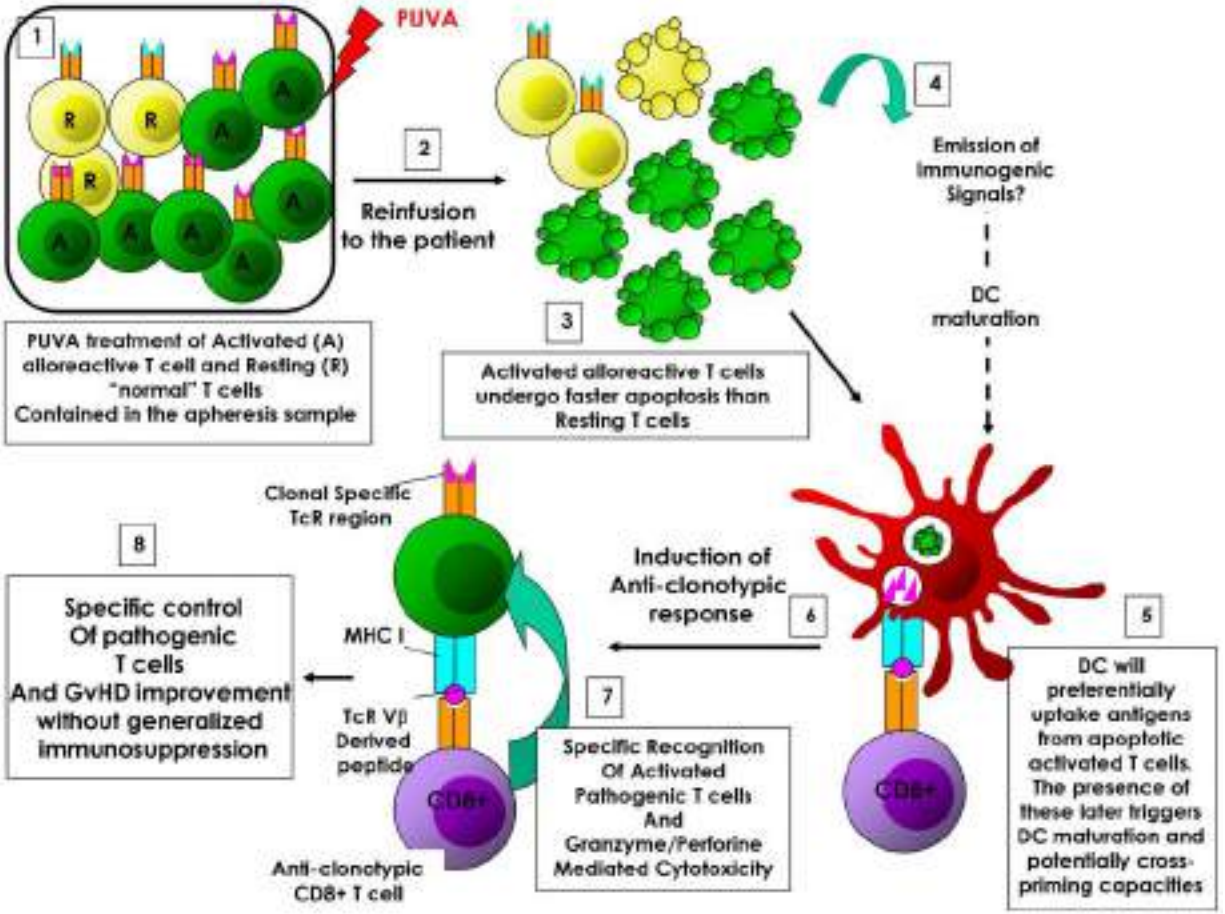
Proposed mechanistic pathways of extracorporeal photochemotherapy



Marshall SR (2006) Technology Insight: ECP for the treatment of GvHD—can we offer selective immune control without generalized immunosuppression? *Nat Clin Pract Oncol* **3:** 302–314 doi:10.1038/ncponc0511

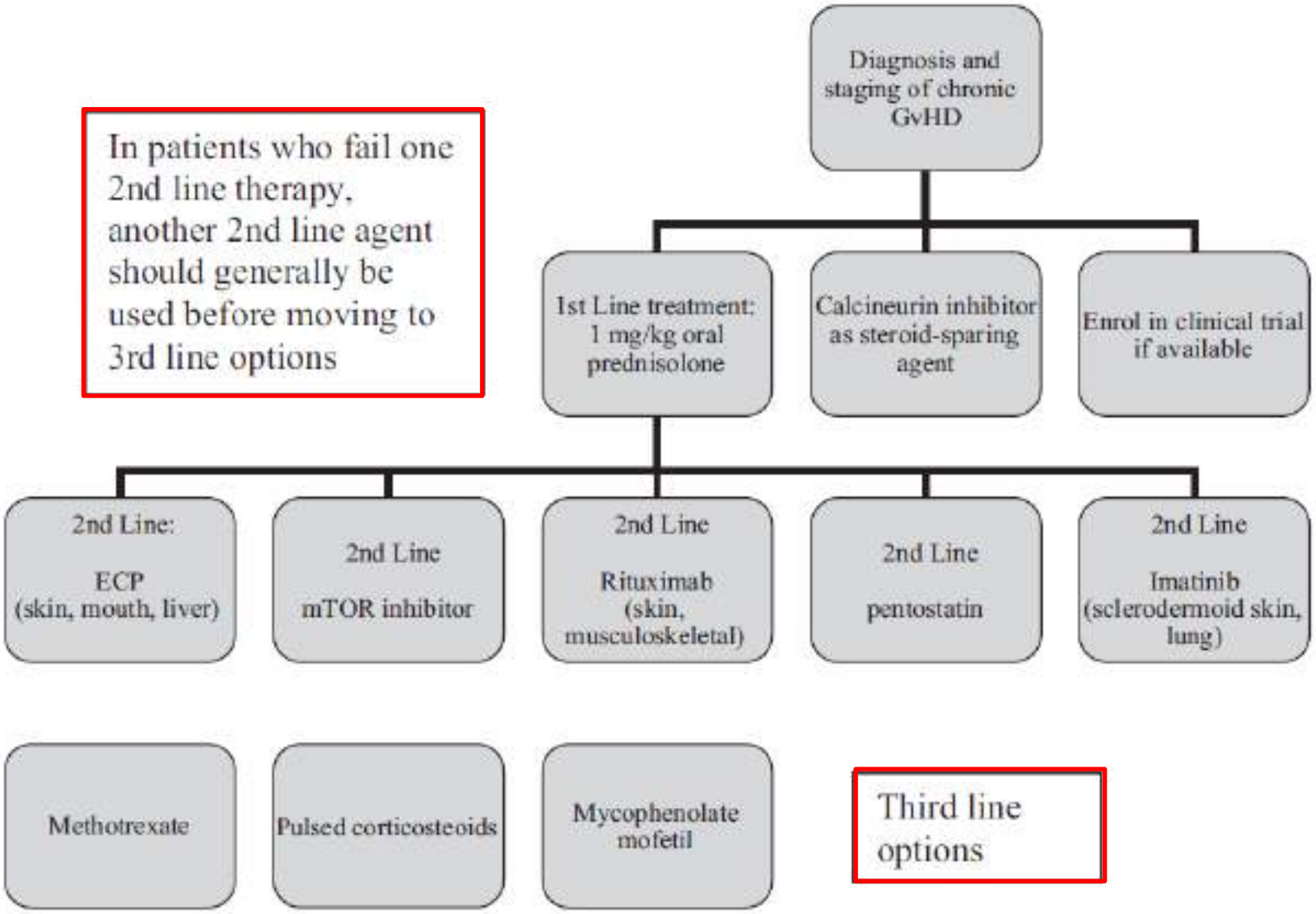
nature CLINICAL PRACTICE ONCOLOGY

ECP στην κορτικο-άντοχη και κορτικο-εξαρτώμενη cGvHD



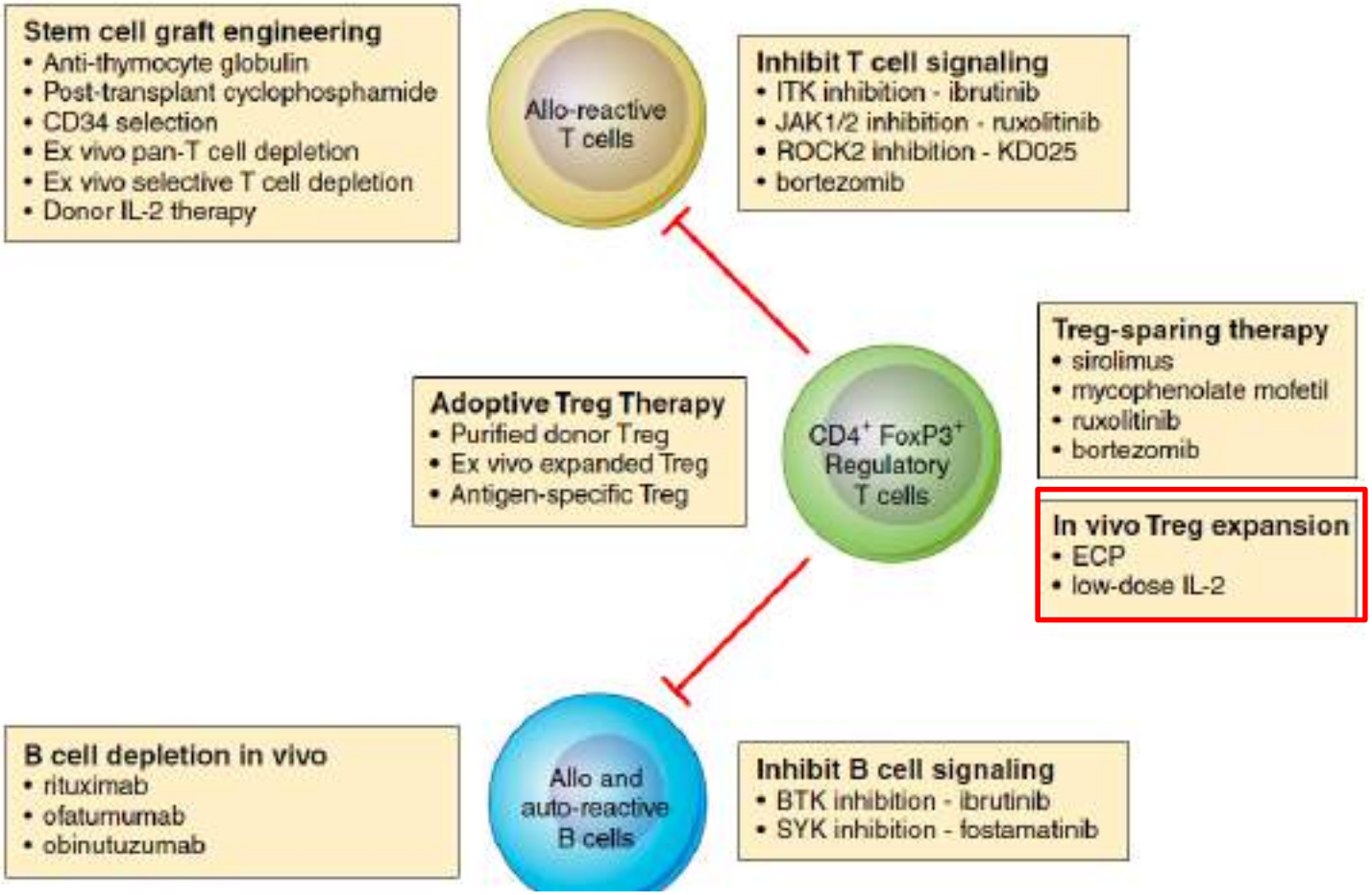
Hannani D. Frontiers Immunology 2017

Diagnosis and management of chronic graft-versus-host disease



British Journal of Haematology
Volume 158, Issue 1, pages 46-61, 26 APR 2012 DOI: 10.1111/j.1365-2141.2012.09128.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09128.x/full#bjh9128-fig-0001

Management of chronic graft-versus-host disease



Cutler CS. Blood 2017

How I treat chronic graft-versus-host disease

Agent	Potential major adverse effects (with major study citations)	Common (>10%) generally less severe adverse effects
Bortezomib	Peripheral neuropathy, thrombocytopenia, malignancy relapse[106]	Herpes virus reactivation
ECP	Vascular access complications[107]	Thrombocytopenia
FAM	New FDA MedWatch warning, warning only applies to azithromycin use in prophylactic (not treatment) setting[108,109]	
Ibrutinib (Imbruvica R)	Pneumonia,[29] impaired platelet function	Fatigue, muscle pain, peripheral edema
Imatinib		Peripheral edema
Interleukin-2	Injection site induration, infections[26]	Constitutional flu-like symptoms
MMF (Cellcept)	Viral reactivation, hypertension, pneumonia, posttransplantation lymphoproliferative disease[110]	GI toxicity, neutropenia, leukopenia
Pamolidomide	Tremor, muscle cramps, peripheral neuropathy[111]	Skin rash
Rituximab (Rituxan R)	Infection, late neutropenia[38,39,112]	B lymphopenia
Ruxolitinib (Jakafi R)	Viral reactivation/infection, bacterial infections[35]	Cytopenias
Sirolimus (Rapamune)	TAM when used in combination with calcineurin inhibitors, renal insufficiency,[113] proteinuria	Peripheral edema, hyperlipidemia, cytopenias

Saratopoulos S, et al. Blood 2019

Transfus Apher Sci. 2012 Apr;46(2):181-8.

Extracorporeal photopheresis in refractory chronic graft-versus-host disease: the influence on peripheral blood T cell subpopulations. A study by the Hellenic Association of Hematology.

Tsirigotis P, Kapsimalli V, Baltadakis I, Kaloyannidis P, Karakasis D, Papalexandri A, Psarra E, Nosi E, Konsta E, Vikentiou M, Papageorgiou S, Sakellari I, Pappa V, Harhalakis N, Anagnostopoulos A, Dervenoulas J.

Μελέτη της επίδρασης της ECP στον αρ. των CD4+, CD8+, CD20+, CD56+ cells, και T-regulatory (Tregs), των naïve, central memory (CM), και effector memory (EM) T-cells

Tregs: στατιστικά σημαντική αύξηση στους 3 μήνες ECP (p=0.015).

CD4+, CD8+ cells: στατιστικώς σημαντικά υψηλότερα σε ασθενείς που ανταποκρίθηκαν στην ECP

→ *η ECP φαίνεται να είναι ανοσο-τροποποιητική παρά ανοσοκατασταλτική*

Transfusion and Apheresis Science 46 (2012) 173–180

Contents lists available at SciVerse ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Extracorporeal photopheresis in the treatment of chronic graft-versus-host disease. The Hellenic experience: A study by the Hellenic association of hematology

Panagiotis Tsirigotis [a,*,1], Panayotis Kaloyannidis [b,1], Apostolia Papalexandri [b], Ioannis Baltadakis [c], Dimitrios Karakasis [c], Ioannis Batsis [b], Ioanna Sakellari [b], Vassiliki Kitra [d], Evgenios Goussetis [d], Sotirios Papageorgiou [a], Alexandros Spyridonidis [e], Stelios Graphakos [d], Nikolaos Harhalakis [c], Ioannis Dervenoulas [a], Achilles Anagnostopoulos [b]

58 ασθενείς με cGVHD ανθεκτική σε τουλάχιστον 1 γραμμή ανοσοκαταστολής

Η ολική απάντηση ήταν **65%**

Tsirigotis P, et al. Transfus Apher Sci. 2012 Apr;46(2):173-80

Extracorporeal photopheresis in the treatment of chronic graft-versus-host disease. The Hellenic experience: a study by the Hellenic association of hematology.

global severity scoring, cGVHD severe 40%

moderate 60%

Σημαντική βελτίωση:	δέρματική	60%
	στόμα	67%
	οφθαλμική	51%
	ηπατική	50%

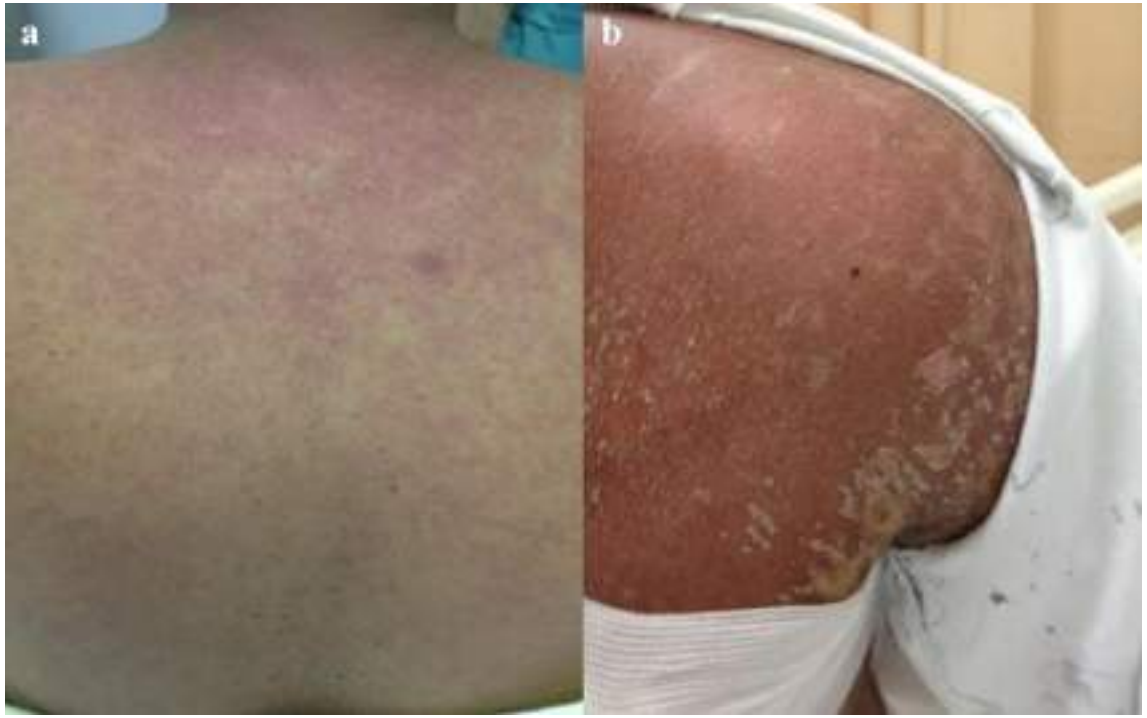
Δm απάντησης: 10 εβδ. (3–16 weeks)

Διακοπή ανοσοκαταστολής: 61% σε Δm 12 m(6–36)

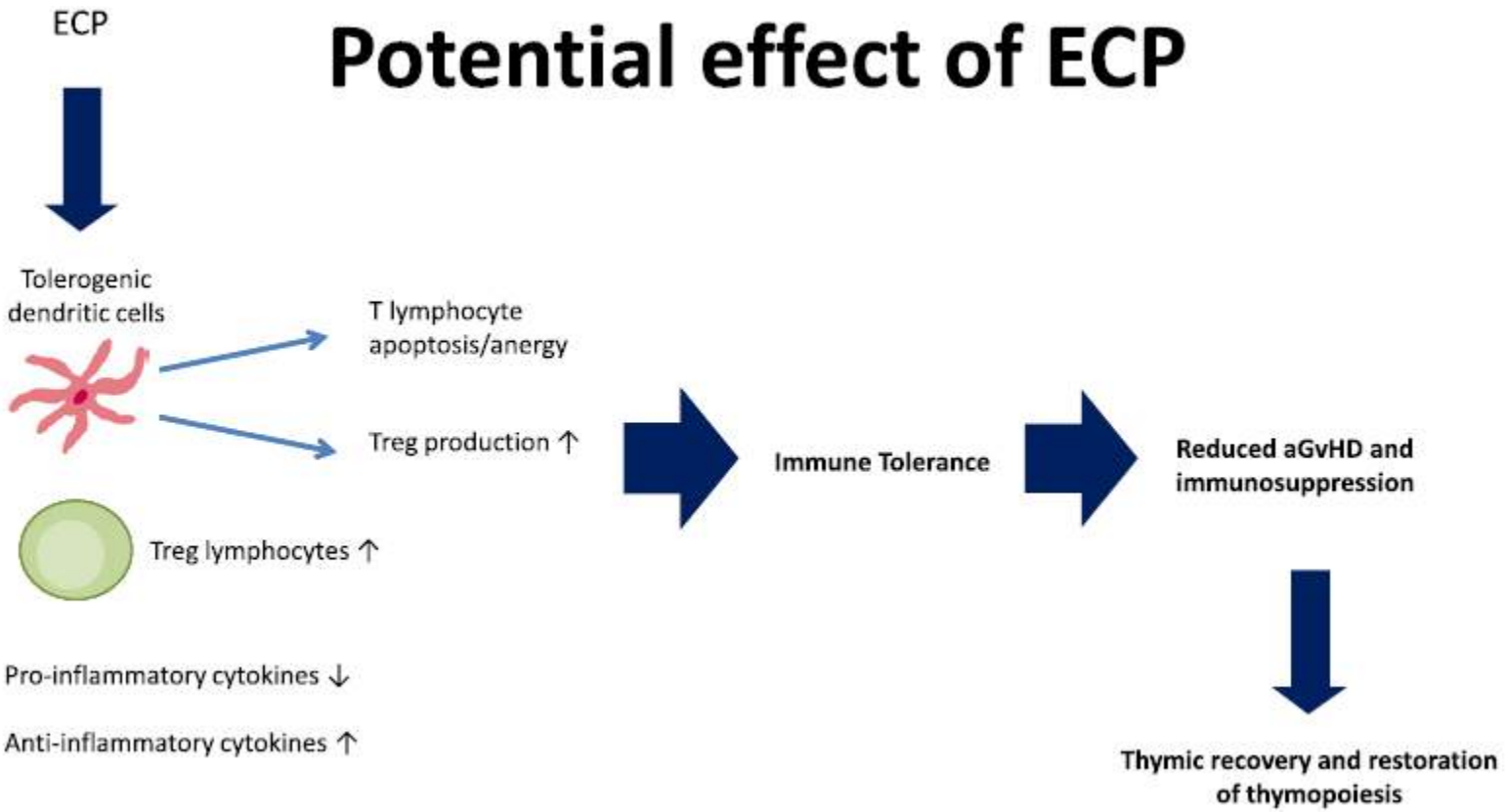
Multivariate analysis.

	RR	CI 95%	Significance
Parameters associated with response to treatment with ECP			
Severity of GVHD moderate vs severe	0.443	0.205–0.955	$p = 0.038$
Parameters associated with discontinuation of immunosuppression			
Response to treatment with ECP yes vs no	5.684	1.250–25.848	$p = 0.019$
Severity of GVHD moderate vs severe	0.277	0.092–0.828	$p = 0.022$
Parameters associated with non-relapse mortality			
Response to treatment with ECP yes vs no	0.212	0.079–0.571	$p = 0.002$
Parameters associated with overall survival			
Response to treatment with ECP yes vs no	7.861	3.084–20.034	$p < 0.001$
Parameters associated with relapse of the original disease			
Response to treatment with ECP yes vs no	0.15	0.030–0.752	$p = 0.021$

Θα μπορούσε η ECP να ωφελήσει και την οξεία GVHD ?



ECP στην aGvHD



Flynn A F1000 Research 2016

Received: 13 April 2018 | Revised: 1 August 2018 | Accepted: 11 August 2018

DOI: 10.1002/jca.21660

WILEY Journal of Clinical Apheresis ASFA

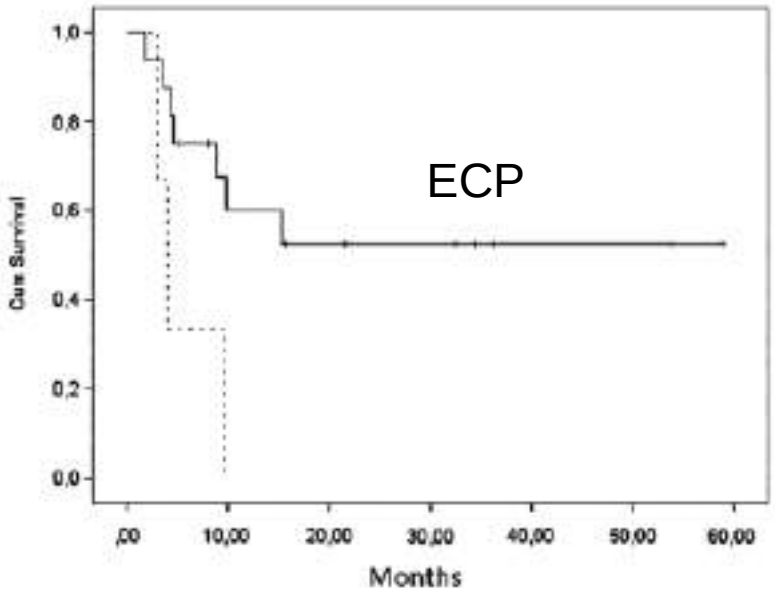
RESEARCH ARTICLE

Favorable impact of extracorporeal photopheresis in acute and chronic graft versus host disease: Prospective single-center study

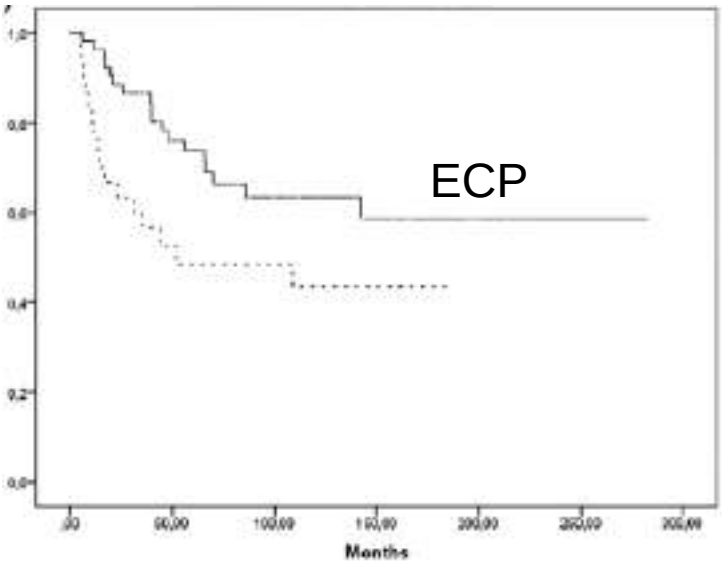
Ioanna Sakellari | Eleni Gavriilaki | Ioannis Batsis | Despina Mallouri | Alkistis-Kira Panteliadou | Andriana Lazaridou | Anna Vardi | Varnavas Constantinou | Evangelia Yannaki | Apostolia Papalexandri | Panayotis Kaloyannidis | Christos Smias | Achilles Anagnostopoulos

Sakellari et al. J Clin Apher 2018

Favorable OS in aGVHD



Favorable OS in cGVHD



Journal of Clinical Apheresis ... ASFA WILEY

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.

Journal of Clinical Apheresis ASFA WILEY

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

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Journal of Clinical Apheresis ... ASFA WILEY

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

Disease	TA modality	Indication	Category	Grade	Page
Graft-versus-host disease (GVHD)	ECP	Acute	II	1C	231
	ECP	Chronic	II	1B	

bjh research paper

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

Acute GvHD	New section, with recommendations on patient selection, treatment schedule, assessment criteria and steroid taper (Appendix S3). Literature review updated to include adults and paediatrics
Chronic GvHD	Update to assessment of response using National Institutes of Health criteria (Lee *et al.* 2015) – Appendix S4

doi: 10.1111/bjh.14537

Journal of Clinical Apheresis ... ASFA WILEY

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

Disease	TA modality	Indication	Category	Grade	Page
Cutaneous T cell lymphoma (CTCL); Mycosis fungoides; Sézary syndrome	ECP	Erythrodermic	I	1B	221
	ECP	Non-erythrodermic	III	2C	

bjh research paper

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

Table II. Changes in the updated consensus statement.

Section	Update in 2016 statement
CTCL	It is recommended that the treatment schedule may be continued in patients with a complete, partial or minimal response as opposed to treatment taper. This is in keeping with other treatments for advanced MF/SS, which should be continued whilst a clinical benefit is derived and cessation of therapy is not recommended whilst a response is durable. This is because there are no curative therapies for CTCL and, in some patients, durable responses >5 years are shown with ECP, which is markedly improved compared to the median survival of advanced stage patients around 3 years (Appendix S2)

doi: 10.1111/bjh.14537

Άλλες ενδείξεις Φωταφαίρεσης

Φλεγμονώδης νόσος εντέρου

Δερματικές νόσοι

Μεταμόσχευση συμπαγών οργάνων

Journal of Clinical Apheresis ... ASFA WILEY

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

Disease	TA modality	Indication	Category	Grade	Page
Inflammatory bowel disease	Adsorptive cytapheresis	Ulcerative colitis/Crohn's disease	III	1B	251
	ECP	Crohn's disease	III	2C	
Nephrogenic systemic fibrosis	ECP/TPE		III	2C	265
Pemphigus vulgaris	TPE	Severe	III	2B	279
	ECP/IA	Severe	III	2C	
Psoriasis	ECP	Disseminated pustular	III	2B	293
	Adsorptive cytapheresis	Disseminated pustular	III	2C	
	TPE	Disseminated pustular	IV	2C	
Scleroderma (Systemic sclerosis)	TPE		III	2C	297
	ECP		III	2A	
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant	ECP		III	2A	199
	IA		III	2C	
	TPE/DFPP		III	2C	

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Disease	TA modality	Indication	Category	Grade	Page
Transplantation, cardiac	ECP	Cellular/recurrent rejection	II	1B	331
	ECP	Rejection prophylaxis	II	2A	
	TPE	Desensitization	II	1C	
	TPE	Antibody mediated rejection	III	2C	
Transplantation, liver	TPE	Desensitization, ABOi living donor	I	1C	337
	TPE	Desensitization, ABOi deceased donor/ Antibody mediated rejection	III	2C	
	ECP	Desensitization, ABOi	III	2C	
	ECP	Acute rejection/Immune suppression withdrawal	III	2B	
Transplantation, lung	ECP	Bronchiolitis obliterans syndrome	II	1C	339
	TPE	Antibody mediated rejection/desensitization	III	2C	

Συμπεράσματα

- Η φωταφαίρεση παραμένει αποτελεσματική θεραπεία 2ης γραμμής για τη cGVHD, ιδιαίτερα με δερματικές βλάβες
- Η πρώιμη εφαρμογή της είναι πολλά υποσχόμενη και για τη aGVHD
- Βελτίωση των τεχνικών μπορεί να συμβάλλει στην ευρύτερη εφαρμογή
- Νέες ενδείξεις ???