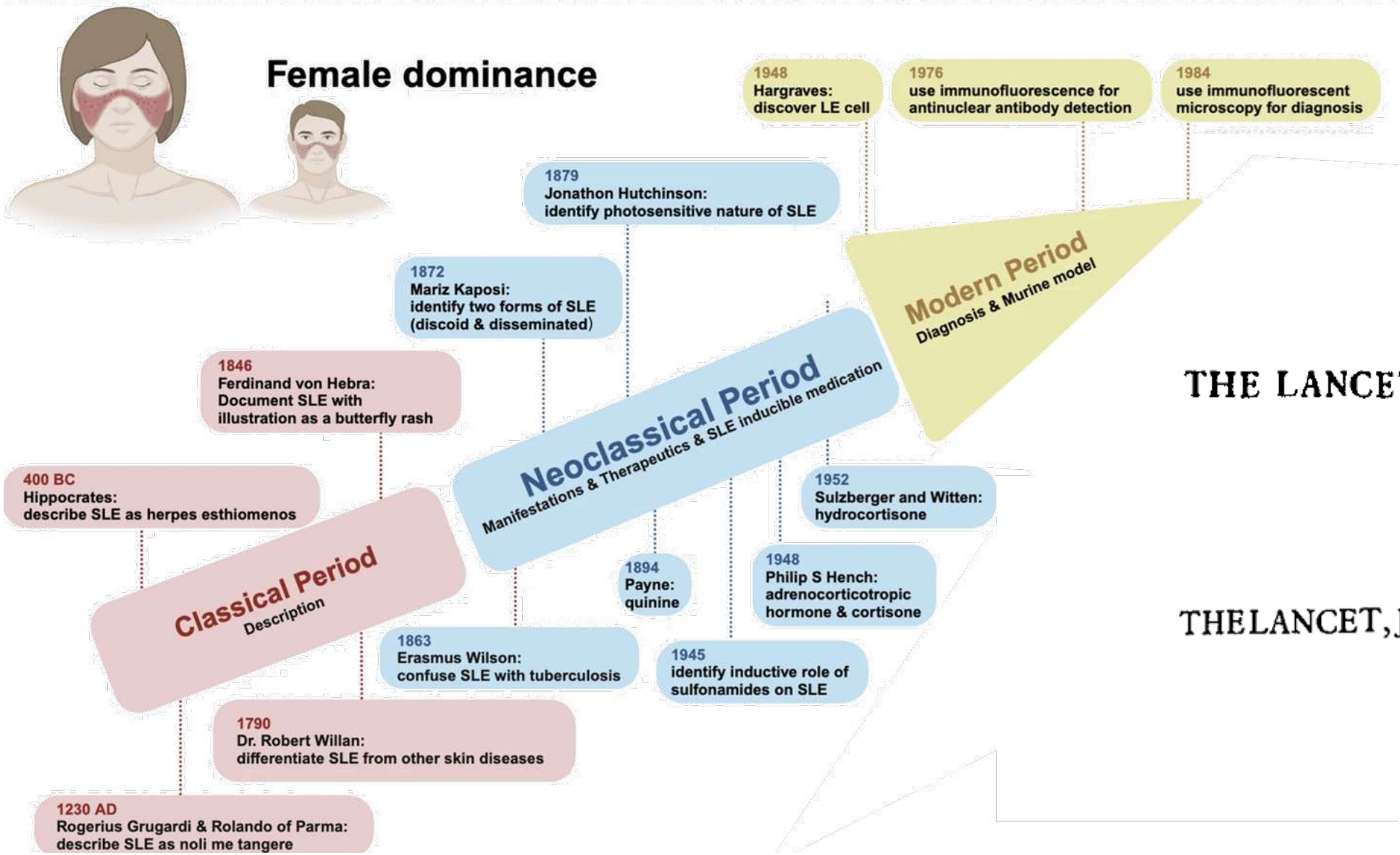
Συστηματικός Ερυθηματώδης Λύκος και Αφαίρεση, που είμαστε σήμερα

Προεδρείο: Ακτσιαλή Μ.
Ομιλήτρια: Κωστοπούλου Μ.

Σύγκρουση συμφερόντων

Καμία για τη συγκεκριμένη ομιλία

Μια παλιά υπόθεση



THE LANCET, APRIL 3, 1976

PLASMAPHERESIS IN THE MANAGEMENT OF ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS?

J. Verrier Jones, R. C. Bucknall, R. H. Cumming, C. M. Asplin

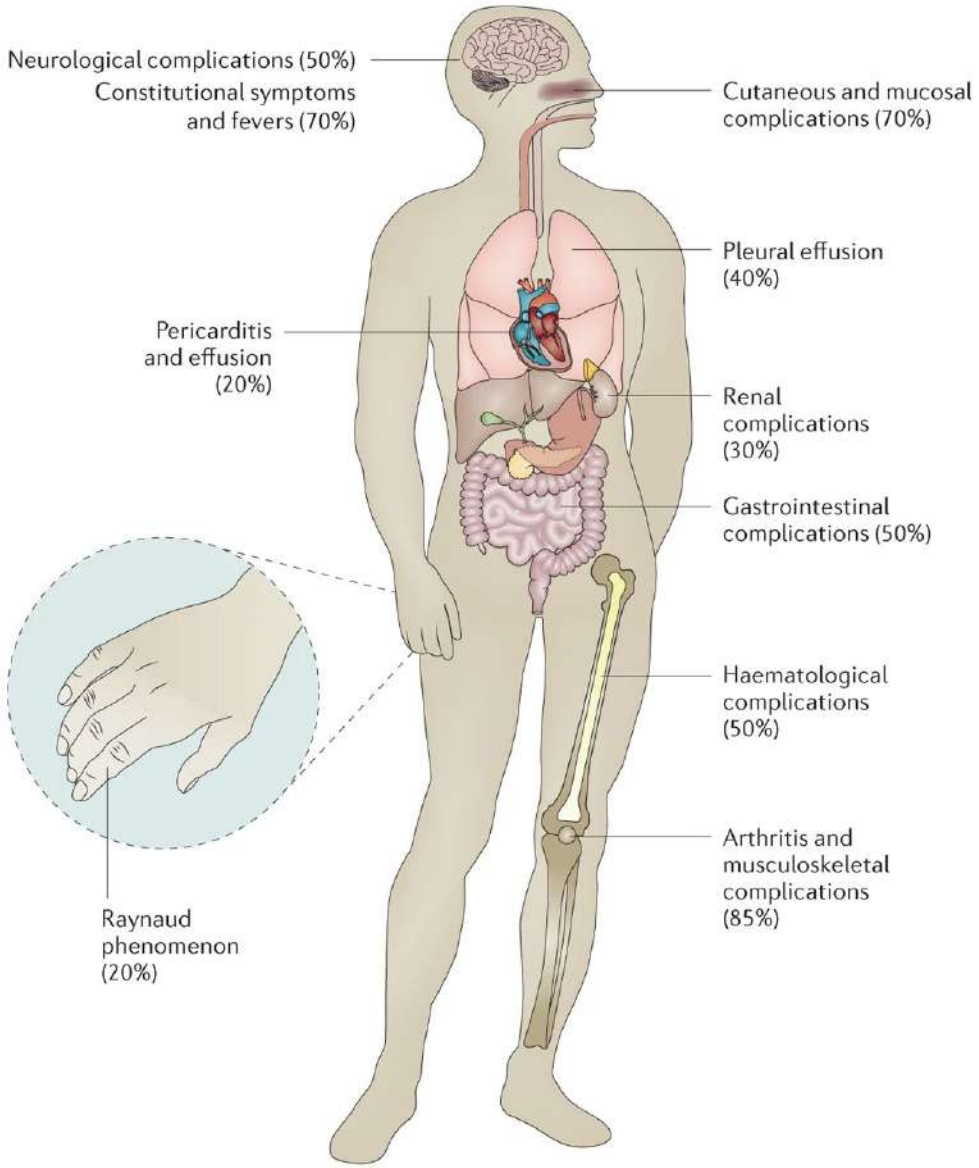
THE LANCET, JANUARY 1/8, 1983

RANDOMISED TRIAL OF PLASMA EXCHANGE IN MILD SYSTEMIC LUPUS ERYTHEMATOSUS

Nathan Wei, David P. Huston, Thomas J. Lawley, Alfred D. Steinberg, John H. Klippel, Russell P. Hall, James E. Balow, John L. Decker

Dai, X et al Sig Transduct Target Ther 10, 102 (2025).

Συστηματικός Ερυθηματώδης Λύκος (ΣΕΛ)



Πολυσυστηματική προσβολή

Συχνότερα **αρθρώσεις** και **δέρμα**

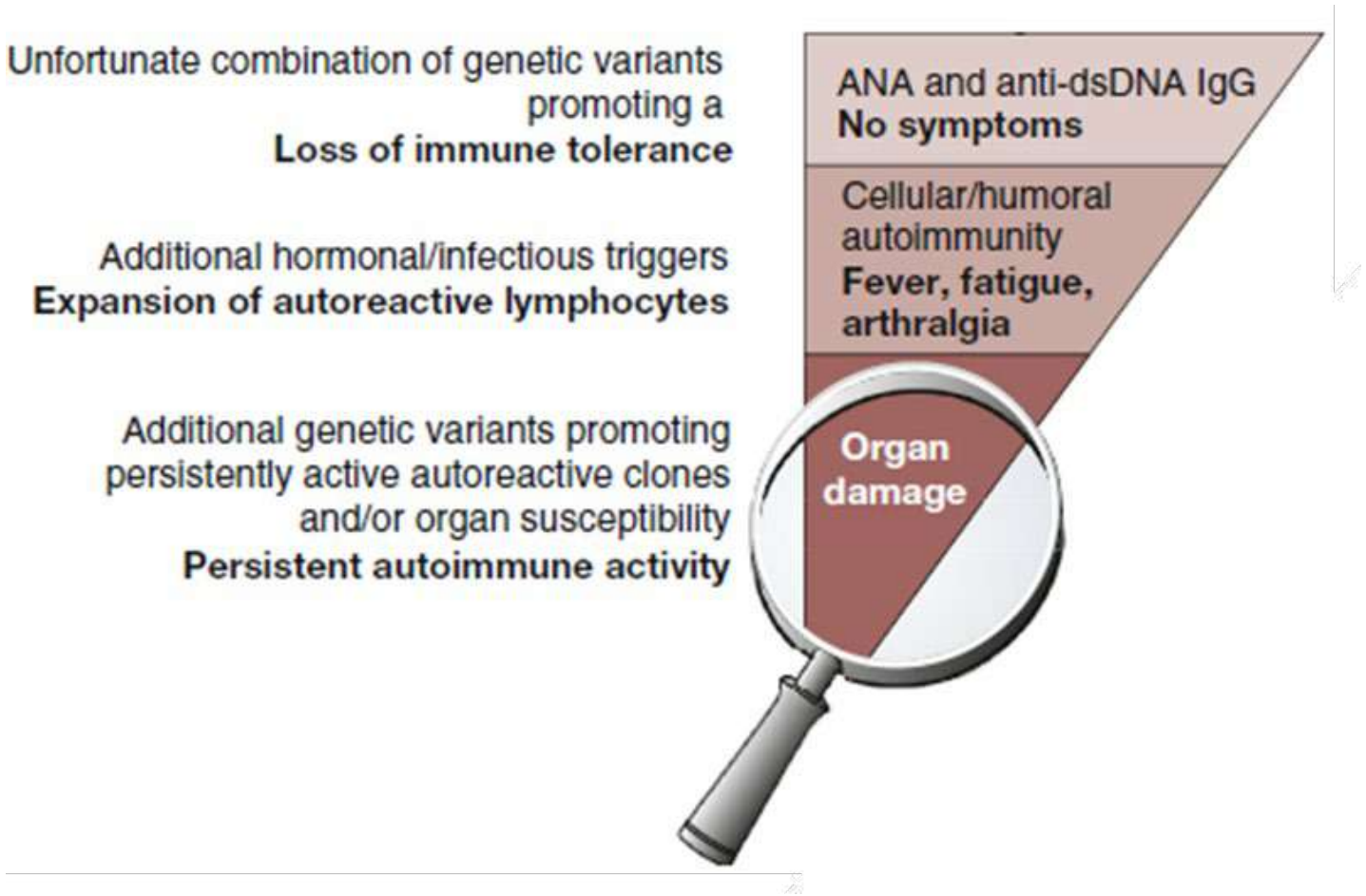
Διάγνωση: κλινικά

60% είχε λάβει άλλη διάγνωση

ΤΡΕ πληθυσμός 0.5-3%

Kaul, A., Gordon, C., Crow, M. et al. Systemic lupus erythematosus. Nat Rev Dis Primers 2, 16039 (2016)

Η παθογένεια του ΣΕΛ



Απώλεια ανοσολογικής ανοχής

↓

Δημιουργία αυτό-αντιδρώντων κλώνων

↓

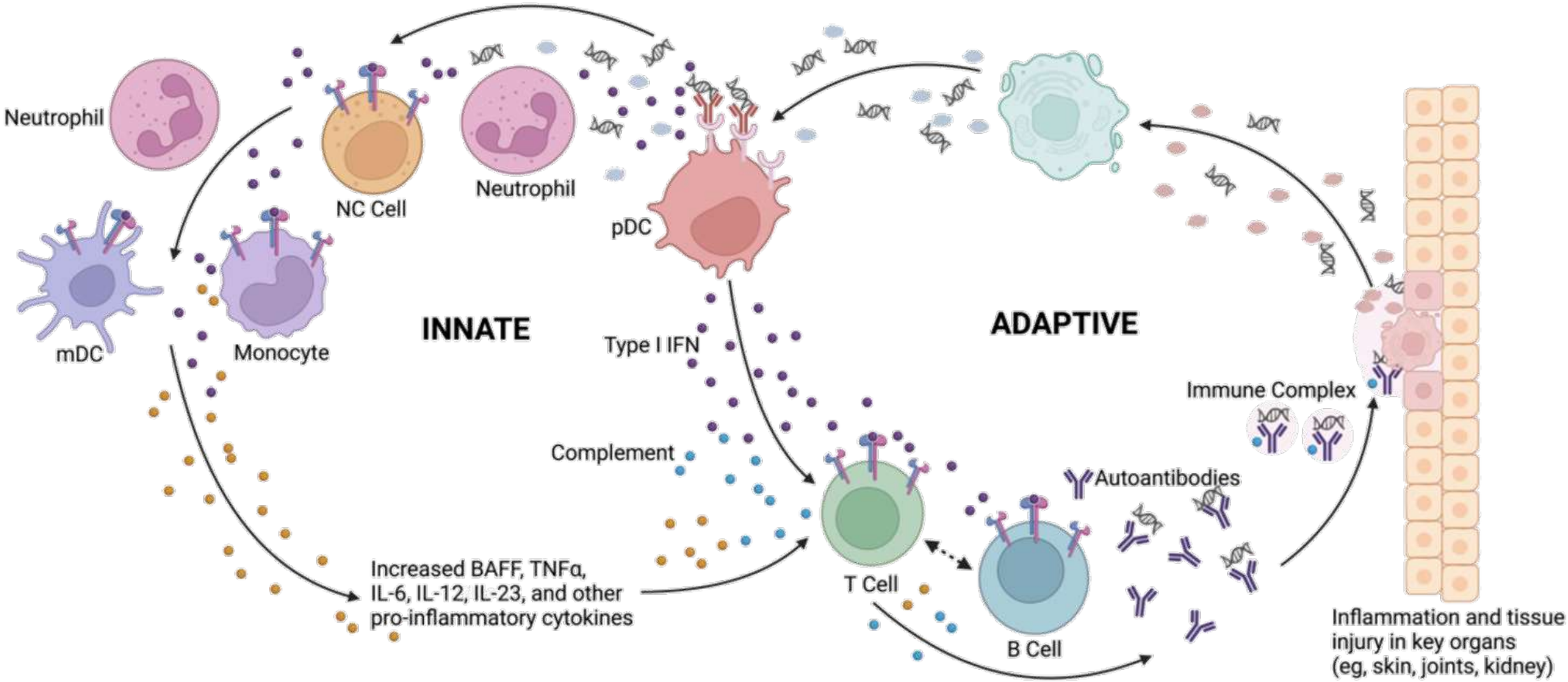
Επέκταση εμμενόντων αυτό-αντιδρώντων κλώνων

↓

Βλάβη οργάνου στόχου

Anders HJ, Rovin B. Kidney Int. 2016;90(3):493-501.

Η παθογένεια του ΣΕΛ



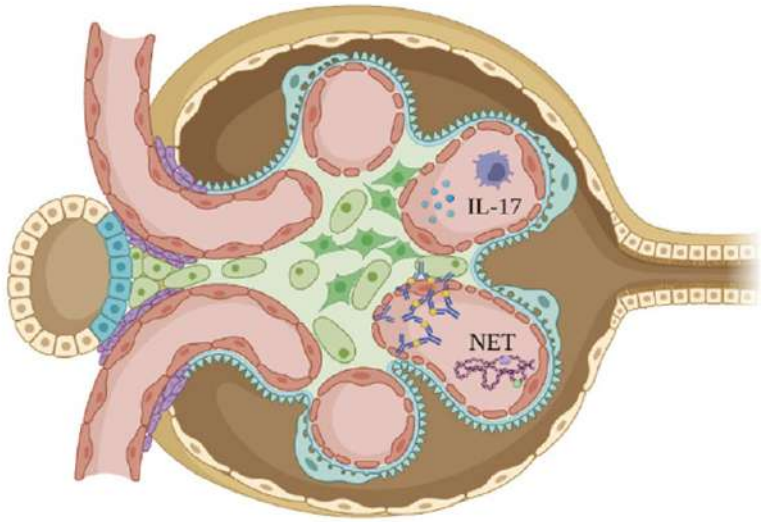
Ουσίες μικρού, μεσαίου και μεγάλου ΜΒ εμπλέκονται στην παθογένεση

Fang J et al. J Cell Immunol. 2024

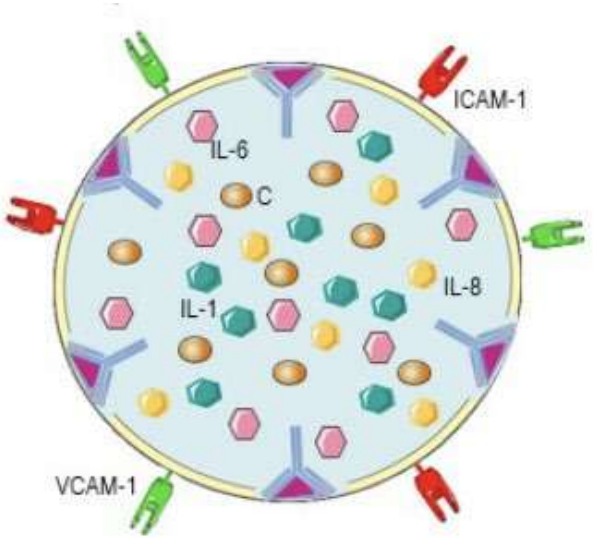
Η παθογένεια του ΣΕΛ

Πρότυπη ανοσοσυμπλεγματική βλάβη

Σπείραμα – Νεφρίτιδα ΣΕΛ



Δέρμα – Αγγειίτιδα ΣΕΛ



Ορογονίτιδα - Περικαρδίτιδα

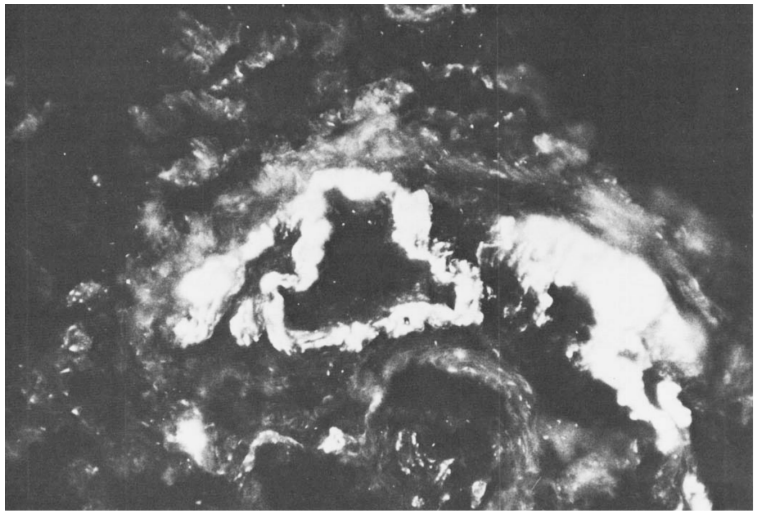


Figure 1. *Immunopathology of pericardial tissue. Area of fluorescence is granular arteriolar staining with anti-sera against IgM, IgG, and C3 (× 100).*

Leone, P et al Lupus Vasculitis: An Overview. Biomedicines 2021
Jacobson et al Arthritis and Rheumatism, Vol. 21, No. 8
(November-December 1978) Yu C, et al. J Autoimmun. 2022 Aug

Η παθογένεια του ΣΕΛ

SLE Organ Involvement	Mainly Cytokine-Driven?	Notes
Neuropsychiatric SLE (inflammatory forms)	**Yes**	CSF IL-6/IFN↑; IC sometimes absent
HLH/MAS, marrow suppression	**Yes**	IFN-γ/IL-18 storm
Fever, fatigue, serositis	**Yes**	IL-1/IL-6/TNF mechanisms
Cutaneous interferonopathies (chilblain, SCLE)	**Yes**	Type I IFN signature
Lupus myositis	**Yes**	IFN-driven myopathy
Lupus nephritis	No	IC & complement classic
Vasculitis	No	IC-mediated
Classic DLE with “full-house” deposition	No	Complement deposition

Υπόθεση αφαίρεσης μορίων που εμπλέκονται στην παθογένεση του ΣΕΛ

Ideal target molecule characteristics for therapeutic plasma exchange

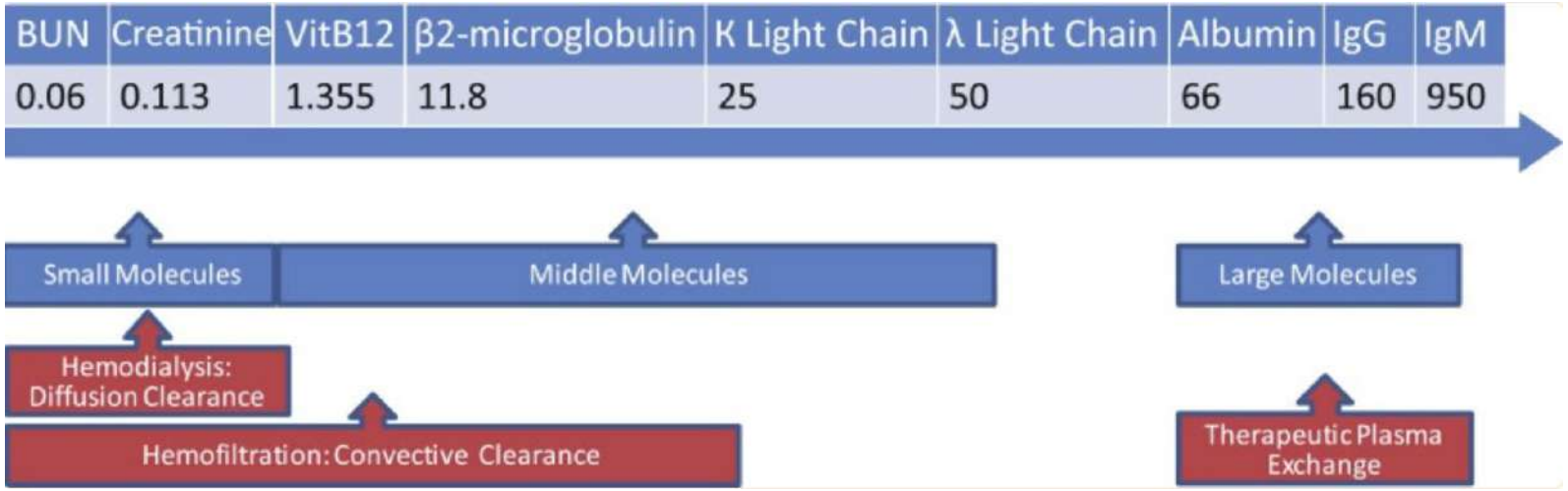
Ideal Target Molecule Characteristic
Identified etiologic agent or toxic substance
High molecular mass (≥15,000 D)
Slow rate of formation
Low turnover
Low volume of distribution

ICs → In situ formation

Complement → ↑formation rate

Cytokines → Small MW

Tertiary germinal centres



Williams M. et al CJASN 2014

Νεφρίτιδα ΣΕΛ και πλασμαφαίρεση

The New England
Journal of Medicine

Volume 326 MAY 21, 1992 Number 21

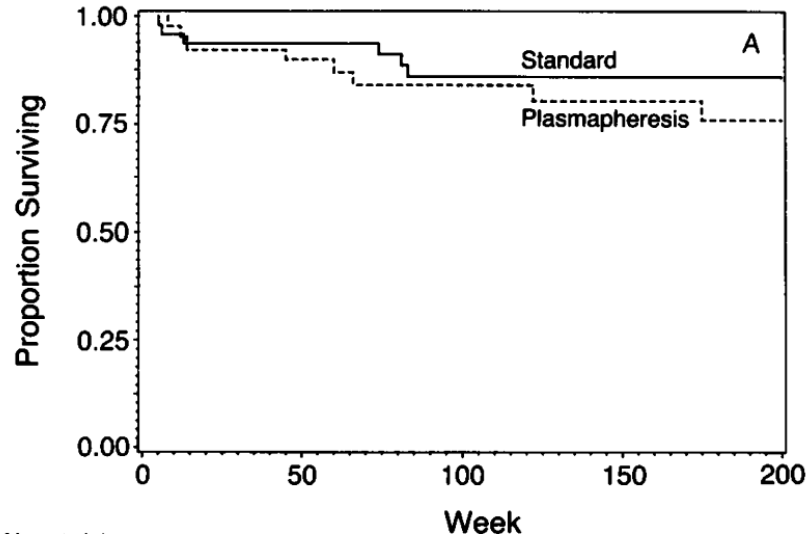
A CONTROLLED TRIAL OF PLASMAPHERESIS THERAPY IN SEVERE LUPUS NEPHRITIS

- RCT (1:1) 86 ασθενείς
- Διάρκεια ΝΛ 1ετος
- Cr 2 mg/dl UPr 5g/d

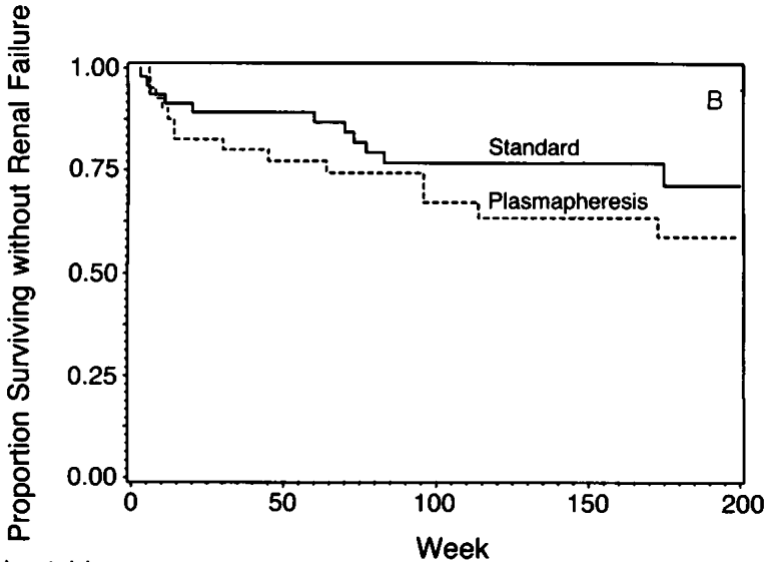
Όλοι έλαβαν po CYC για τουλάχιστον 2(!!!) μήνες + GCs

PLEX (3/w for 1 month) vs placebo

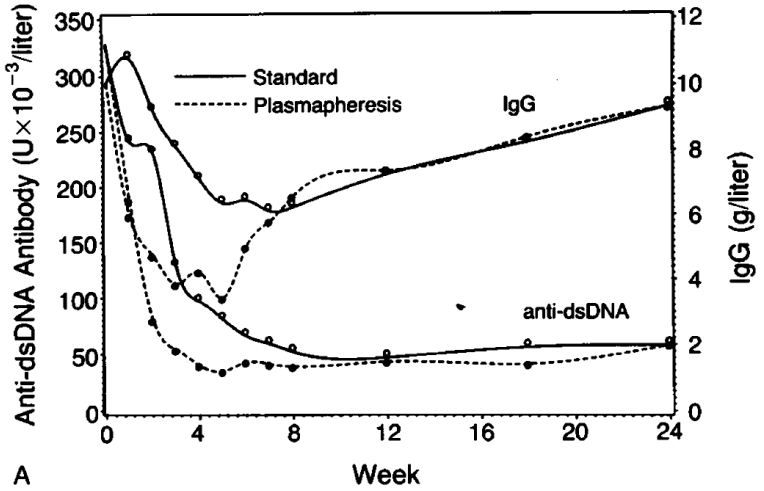
Συνολική επιβίωση



Συνολική και νεφρική επιβίωση



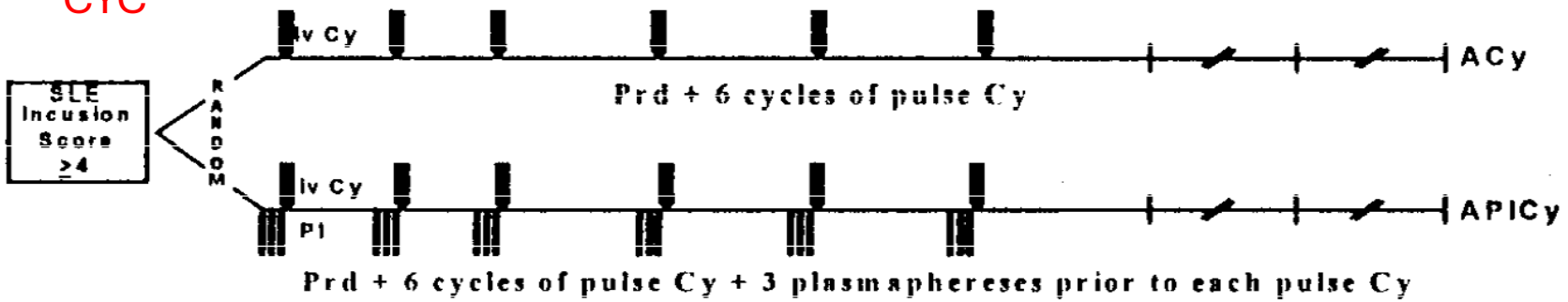
Anti-ds DNA



Lewis EJ et al N Engl J Med. 1992

Νεφρίτιδα ΣΕΛ και πλασμαφαίρεση

CYC



3 PLEX + CYC

- 19 pts
- Cr 1.5 mg/dl
- UPr 8g/d

- PLEX+ CYC vs CYC

TABLE II. Study Parameters at Entry, 6 and 24 Months (+1 S.D.)*

Parameter	Entry	6 months	24 months	$P < .025$
Cyclosphosphamide group				
Serum creatinine (mg/dl)	1.35 ± 0.61	1.22 ± 0.40	2.72 ± 3.04	ns
Anti-DNA (IU)	709.67 ± 1,661.6	153.44 ± 405.07	38.78 ± 64.39	ns
24-hour urine protein (G)	8.64 ± 0.84	6.10 ± 5.09	4.43 ± 6.54	ns
Pulse/synchronization group				
Serum creatinine (mg/dl)	1.52 ± 0.4	1.31 ± 0.3	2.02 ± 1.79	ns
Anti-DNA (IU)	424 ± 938.9	24.67 ± 23.86	29.63 ± 32.96	.01
24-hour urine protein (G)	8.29 ± 0.93	6.91 ± 1.5	5.18 ± 5.47	ns

Wallace DJ,et al. J Clin Apher. 1998

Νεφρίτιδα ΣΕΛ και πλασμαφαίρεση

Journal of Clinical Apheresis 17:72–77 (2002)

Synchronised Therapy and High-Dose Cyclophosphamide in Proliferative Lupus Nephritis

- Non- RCT
- 12 ασθενείς 3xPLEX και iv CYC (μηνιαία για 6 μήνες)
- 16 ασθενείς μόνο iv CYC (μηνιαία για 6 μήνες)
- **Cr 1.3-1.4 mg/dl UPr 2.5 g/d**

Complete remission at the end of the treatment period and end of follow-up

Time/Treatment	PLEX + CYC	CYC
6 months	75%	31%
4 years	41%	50%

TABLE III. Occurrence of Adverse Effects During the Study Period

	Group I ($n=12$) (%)	Group II ($n=16$) (%)
Persistent hypogammaglobulinemia	4/12 (33)	4/16 (25)
Transient thrombocytopenia	3/12 (25)	
Permanent leukopenia		1/16 (6.2)
Sustained amenorrhea	3/12 (25)	3/16 (18.7)
Carcinoma of the cervix		1/16 (6.2)
Herpes zoster	1/12 (8.3)	
Septic arthritis of the knee	1/12 (8.3)	

Danieli et al Journal of Clinical Apheresis 17:72±77 (2002)

Νευροψυχιατρικός ΣΕΛ και πλασμαφαίρεση

The Role of Plasmapheresis in the Treatment of Severe Central Nervous System Neuropsychiatric Systemic Lupus Erythematosus

C. Michael Neuwelt

First published: 15 May 2003 | https://doi-org.proxy.kib.ki.se/10.1046/j.1526-0968.2003.00032.x | Citations: 71

SECTIONS PDF TOOLS SHARI

Abstract

Abstract: Twenty-six patients, who received plasmapheresis (PP) either alone or synchronized with cyclophosphamide (IV-CYC/PP), are retrospectively reviewed from Medline searches and personal experience from 1976 to 2002. Patients with central nervous system neuropsychiatric systemic lupus erythematosus (CNS-NPSLE) were evaluated according to the American College of Rheumatology (ACR) case definitions of 1999. Eleven of the patients were under the age of 21 years (range 7–21 years), highlighting the need for an aggressive treatment option for young patients who are refractory to other treatments. After treatment with PP or IV-CYC/PP, 74% of patients improved, 13% stabilized, and 13% progressed. Major side-effects occurred from central

Η μεγαλύτερη σειρά 26 ασθενείς

Αθηρωματική < Φλεγμονώδης

Καταστροφικό APS

Table 3
Treatment combinations[a].

	No. N = 522 episodes	%
Individual treatments		
AC	427	82
Cs	398	76
PE	181	35
IVIG	141	27
CYC	126	24
RTX	33	6
Eculi	2	0.2
Treatment combinations		
AC + CS	101	19
AC + CS + PE and/or IVIG	96	18
AC alone	64	12
AC + CS + PE	52	10
AC + CS + IVIG	44	8
AC + CS + CYC	34	7
AC + CS + PE + CYC	28	5
AC + CS + IVIG + CYC	20	4

Σε ποσοστό 35% έγινε TPE

30% σχετιζόμενο με SLE

I. Rodríguez-Pintó et al. / Autoimmunity Reviews 15 (2016) 1120–1124

Θρομβωτική μικροαγγειοπάθεια (TMA) και πλασμαφαίρεση

TMA με θετικά aPL

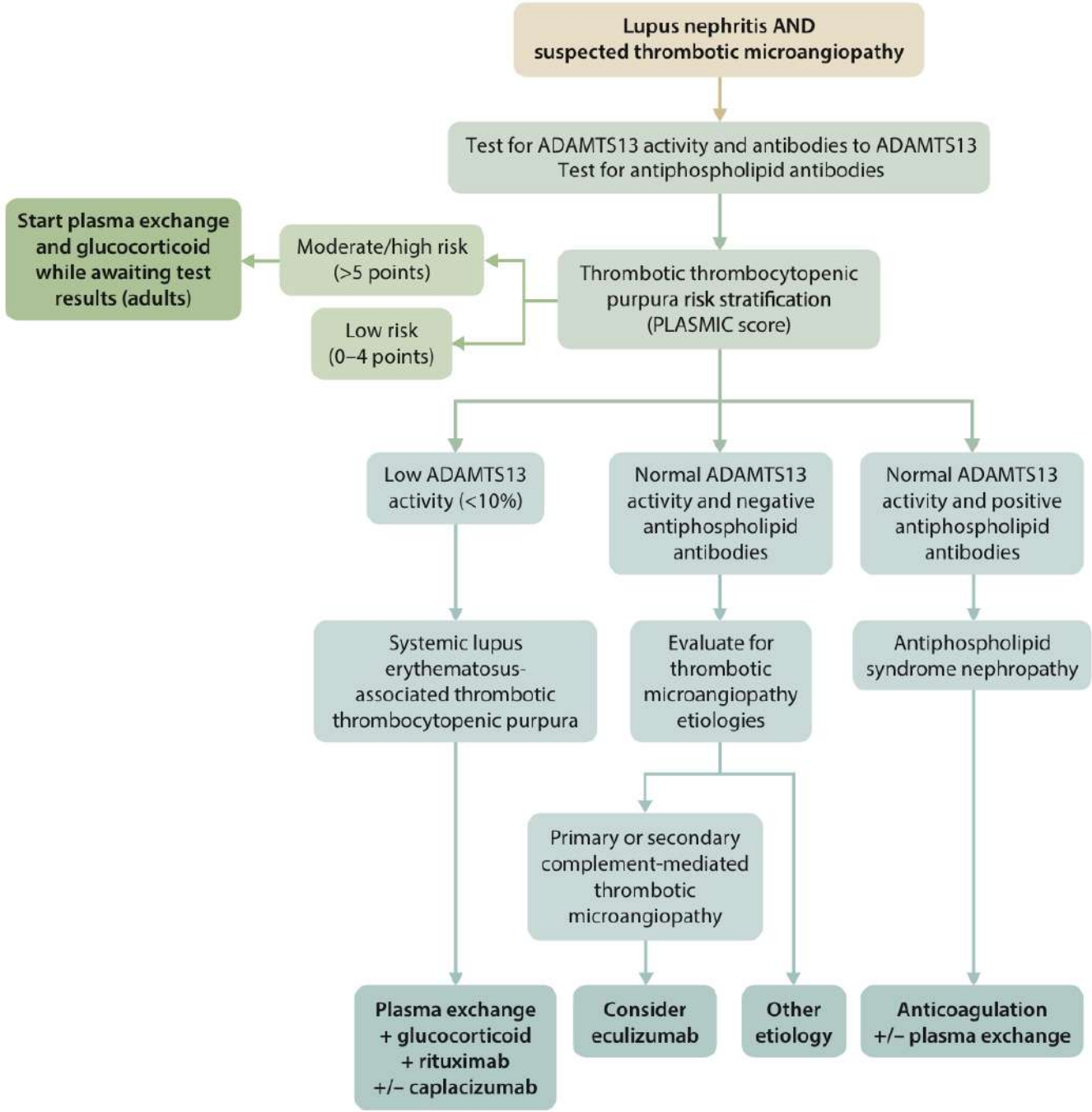
TMA χωρίς aPL (ttp/hus, κακοήθης υπέρταση, σκληρόδερμα, renal-limited)

Plasmapheresis Is Associated With Better Renal Outcomes in Lupus Nephritis Patients With Thrombotic Microangiopathy

A Case Series Study

70 pts με νεφρίτιδα ΣΕΛ και TMA

Μόνο 9 έλαβαν TPE με καλά αποτελέσματα



KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES ®
KDIGO

PLASMIC Score

Parameter	Result	Score
Platelet count	<30K	1
Creatinine	<2.0	1
INR	<1.5	1
MCV	<90	1
Presence of hemolysis variable	Either: -Retic>2.5% -Undetectable hapto-globin or -iBili>2 mg/dL	1
Abscence of active cancer		1
No prior stem cell or organ transplant		1

Πνευμονική (διάχυτη κυψελιδική) αιμορραγία και πλασμαφαίρεση

- Ένδειξη έμμεση από άλλα πνευμονονεφρικά

Difuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 1997;

4 ασθενείς 2 πέθαναν

Κύηση στο ΣΕΛ και πλασμαφαίρεση

- Συμβατή με κύηση
- Αντιμετώπιση έξαρσης ΣΕΛ
- Προετοιμασία κύησης σε APS ασθενείς με πολλαπλές αποβολές
- Anti-Ro με κλινική εικόνα κκ αποκλεισμού σε μητέρα

❖ Υπεργλοιότητα και κρυοσφαιρίνες

Φάρμακα στο ΣΕΛ και πλασμαφαίρεση

Corticosteroids before or after PEX

Cyclophosphamide (IV or oral) before or after TPE.

Mycophenolate mofetil / azathioprine before or after TPE

Rituximab (anti-CD20 mAb) High molecular weight (145 kDa) but highly plasma-bound; significant removal if PEX is done soon after infusion Critical: perform PEX ≥72 h after rituximab infusion.

Belimumab (anti-BLyS mAb) Similar to rituximab — large, protein-bound

Calcineurin inhibitors (cyclosporine, tacrolimus) Lipophilic, protein-bound; limited data but possible removal

ΣΕΛ και ανοσοπροσρόφηση

Table 2. Immunoadsorption in systemic lupus erythematosus (adopted from Stummvoll G, *NephroScript* 2007; 2:34)

Ligand/device	Patient (*n*)	Investigated parameter
IgG-Therasorb	16	Proteinuria, disease activity, dsDNA in lupus nephritis
	16	Infection, disease activity, dsDNA
	2	Outcome of pregnancy in active SLE
	1	Proteinuria, dsDNA in lupus nephritis with active tuberculosis
	2	Infection, dsDNA, IgG in SLE with/without immunoglobulin substitution
Protein A/Prosorba, Immunosorba	8	dsDNA, IgG
Dextran sulphate/Selesorb	1	Renal function in class IV lupus nephritis
	1	Clinical improvement in dermal vasculitis
	19	Disease activity, dsDNA
	6	Proteinuria, disease activity, dsDNA in lupus nephritis
	6	dsDNA, disease activity
Phenylalanine/Immusorba	6	dsDNA, proteinuria in lupus nephritis
	50	Disease activity
	10	Disease activity, dsDNA (comparison to the Therasorb device)
C1q	8	Proteinuria, renal function, arthritis, dermal vasculitis

A. *Kronbichler et al. / Autoimmunity Reviews 15 (2016) 38–49*
B. *Schwenger et al Nephrol Dial Transplant (2010) 25: 2407–2413*

ΣΕΛ και ανοσοπροσρόφηση

Immunoadsorption and plasmapheresis are equally efficacious as adjunctive therapies for severe lupus nephritis

Chee-Yean Loo, Mohd Shahrir Mohamed Said *, Rozita Mohd, Abdul Halim Abdul Gafor, Rashidi Saidin, Norma Abdul Halim, Mei Kwi Chua, Norella C.T. Kong

Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia

ARTICLE INFO

Keywords:
Severe lupus nephritis
PP
IA
SLEDAI score

ABSTRACT

This was a prospective randomized controlled trial to evaluate the effects of immunoadsorption (IA) versus conventional PP (PP) as adjunctive therapy in the treatment of severe lupus nephritis (LN).

Of 28 patients with biopsy-proven severe LN (ISN/RPS classes III or IV ± V), 14 underwent 36 sessions of PP and the other 41 sessions of IA in addition to our center's standard LN treatment protocol. Three patients in the PP group and 2 in the IA group experienced a transient, marked drop in platelets with the second session. Except for a higher pre treatment mean SLEDAI score in the PP group 17.4 ± 2.0 vs. 13.5 ± 4.8; $p = 0.009$ and a serum creatinine of 163 ± 7.9 vs. 81.7 ± 10.2; $p = 0.33$, there were no other baseline differences. Some differences did exist between the two therapies in the immediate post-treatment phase, at 1 and 3 months. Three in IA relapsed, none of PP in third months, whereas two patients relapsed in the PP and none of IA cohorts at 6 months. However, most of these parameters did not differ by 6 months. The pre- and post-therapy SLEDAI scores remained different 12.4 ± 4.5 vs. 9 ± 4; $p = 0.04$ at 1 month, and at 3 month 13.5 ± 4.7 vs. 7.7 ± 1.1; $p = 0.012$ but not at 6 months.

RCT 28pts

1:1 TPE vs IA (+ IS)

Κρεατινίνη ορού

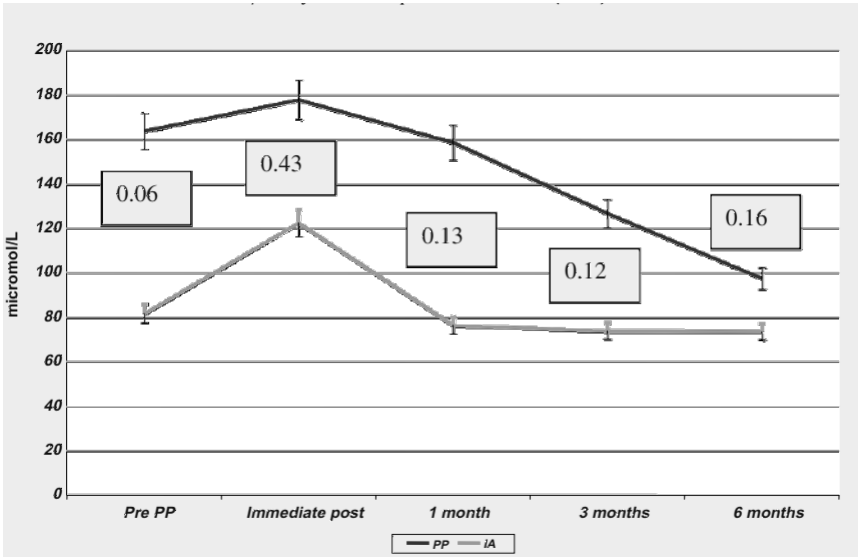


Fig. 4. Effects of pheresis on serum creatinine.

C.-Y. Loo et al. / Transfusion and Apheresis Science 43 (2010) 335–340 339

Meta- analysis on the efficacy and safety of immunoadsorption in SLE

Laboratory parameters	Number of studies	MD (95% CI)	*P* value
IgG	16	- 1.22, (- 1.69, - 0.75)	*P* < 0.001
C3	13	0.72, (0.56, 0.87)	*P* < 0.001
C4	7	0.75, (0.23, 1.27)	*P* = 0.005
anti-dsDNA	10	- 1.64 ,(- 2.70, - 0.59)	*P* = 0.002
Scr	14	- 0.97, (- 1.30, - 0.65)	*P* < 0.001
24-h urine protein	12	- 1.09, (- 1.79, - 0.39)	*P* = 0.002

Incidence of adverse effect	Number of studies	RR (95% CI)	*P* value
Fever or chills	3	7.79, (1.53, 39.68)	*P* = 0.014
Puncture point bleeding	2	8.00, (1.05, 60.87)	*P* = 0.045
Thrombocytopenia	2	4.15, (0.92, 18.64)	*P* = 0.063
Bleeding risk	3	6.66, (1.60, 27.76)	*P* = 0.009

Ασιατικός πληθυσμός

Διαφορετικές ενδείξεις

Διαφορετικά πρωτόκολλα

Διαφορετικά control groups

Ασφάλεια;

Long-term?

Yang, M et al. Clin Rheumatol 39, 3581–3592 (2020)

68 SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence: 0.3 to 31.5/100,000 person-years

Indication	**Procedure**		**Category**	**Grade**
Severe*	TPE		II	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1 (20)	2 (108)	>10 (>200)	NA

*Refractory and/or organ failure= diffuse alveolar hemorrhage, thrombotic microangiopathy, hyperviscosity, cryoglobulinemia, cytopenias, severe neuropsychiatric involvement and catastrophic antiphospholipid syndrome.

Volume treated: 1 to 1.5 TPV

Replacement fluid: Albumin, plasma

Frequency: LN or DAH: daily or every other day; other severe disease conditions: 1 to 3 times per week

Σε άλλες οδηγίες (EULAR, KDIGO) η πλασμαφαίρεση έχει θέση στο **ΣΕΛ μόνο σε συνύπαρξη με ΤΜΑ**

68.5 Duration and discontinuation/number of procedures

Typically, a course of 3 to 6 TPE is appropriate to see response in patients with refractory disease and/or severe complications of SLE. Prolonged treatments have been reported but efficacy and indication of this approach are questionable

Sanchez AP, et al J Clin Apher. 2023

Συστηματικός Ερυθηματώδης Λύκος και Αφαίρεση, που είμαστε σήμερα

Είμαστε εκεί που ήμασταν χωρίς ισχυρά νέα δεδομένα που να επεκτείνουν την εφαρμογή της στο ΣΕΛ

Επαναληπτικές RCTs σε νεφρίτιδα απέτυχαν να δείξουν όφελος

Περιορισμένα δεδομένα με καλά αποτελέσματα κυρίως σε case series/reports για νευροψυχιατρικό, CAPS, DAH

Πιο ισχυρά δεδομένα (πάλι μέτριας ποιότητας) για τη χρήση της σε συνύπαρξη με TMA (TTP/HUS, APS etc)

Καλύτερα αλλά περιορισμένα αποτελέσματα από τη χρήση της ανοσοπροσρόφησης

Καλό προφίλ ασφαλείας

Η πολυπαραγοντική παθογένεση της νόσου ενδεχομένως να εξηγεί την μέτρια αποτελεσματικότητα.
Μένει αδιευκρίνιστο αν υπάρχει πρώιμο όφελος (βλ αγγειίτιδες)