TREATMENT OF THE ANTIPHOSPHOLIPID SYNDROME: MY TEN TOP TIPS

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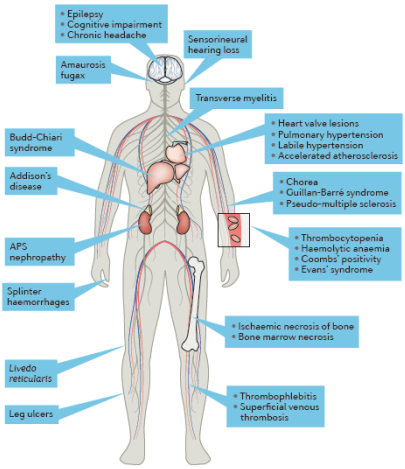
XVth UCLouvain Review Course on Systemic Rheumatic Diseases
December 4, 2021

Antiphospholipid syndrome (APS): some facts

- Most common acquired thrombophilia
- 10-20% of recurrent miscarriage
- Responsible for 1:5 strokes in under 50s
- Up to 30-40 % of patients with SLE have aPL but not all get APS

Ruiz-Irastorza G, Lancet. 2010
Schreiber K, Nat Rev Dis Primers. 2018
Sciascia S, Ann Rheum Dis 2015

Extra-criteria manifestations of antiphospholipid syndrome



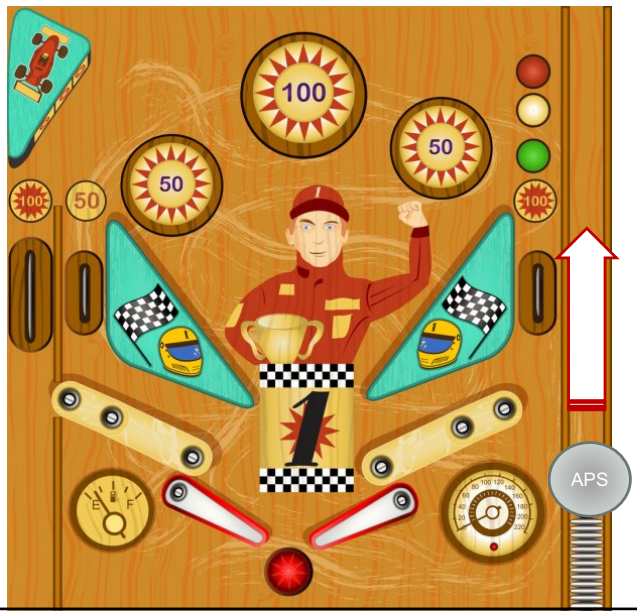
Non-thrombotic clinical manifestations frequently observed in association with the presence of aPL

→ a significant negative impact on prognosis or morbidity

- Leg ulcers
- Thrombocytopenia
- Haemolytic anaemia
- Heart valve lesions
- Pulmonary hypertension
- Headache
- Cognitive disorders
- Transverse myelitis

•Sciascia S, et al. Nat Rev Rheumatol 2017

Tailored therapy in APS



Tailored therapy in APS

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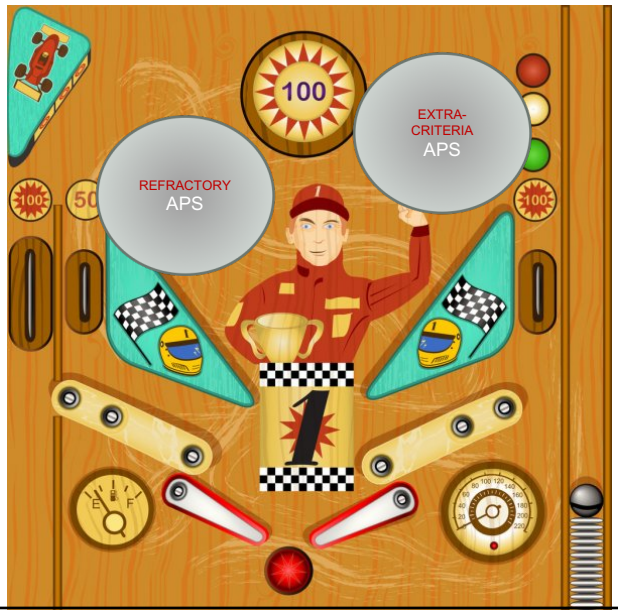

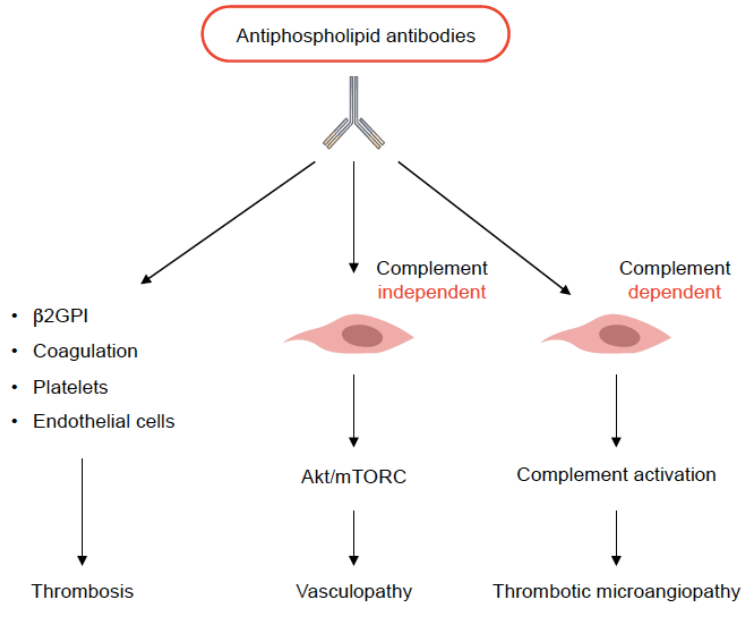

TAILORING TREATMENT IN APS

- DOAC
- HCQ
- IVIG
- ANTI-COMPLEMENT
- TARGETING mTOR signaling
- ANTI-CD20
- ANTI-BAFF
- CD38-TARGET THERAPIES

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Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

Hannah Cohen, Beverley J Hunt, Maria Efthymiou, Deepa R J Arachchillage, Ian J Mackie, Simon Clawson, Yvonne Sylvestre, Samuel J Machin, Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline J Doré, Munther Khamashta*, David A Isenberg*, for the RAPS trial investigators

116 patients w previous VTE, confirmed APL on standard-intensity warfarin, randomised to continue or rivaroxaban (n=56)

Primary outcome – laboratory assay of thrombin generation differed between anticoagulants, no difference in activation markers (D-dimer, TAT, P1+2)

Serious AEs in 4 of each group, no thrombosis or major bleeding seen in either group. Study suggests rivaroxaban is a suitable alternative in this type of APL patient

Cohen et al Lancet Haematol 2016

blood®

MENU

CLINICAL TRIALS AND OBSERVATIONS | SEPTEMBER 27, 2018

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Clinical Trials & Observations

Vittorio Pengo, Gentian Denas, Giacomo Zoppellaro, Seena Padayattil Jose, Ariela Hoxha, Amelia Ruffatti, Laura Andreoli, Angela Tincani, Caterina Cenci, Domenico Prisco, Tiziana Fierro, Paolo Gresele, Arturo Cafolla, Valeria De Micheli, Angelo Ghirarduzzi, Alberto Tosetto, Anna Falanga, Ida Martinelli, Sophie Testa, Doris Barcellona, Maria Gerosa, Alessandra Banzato

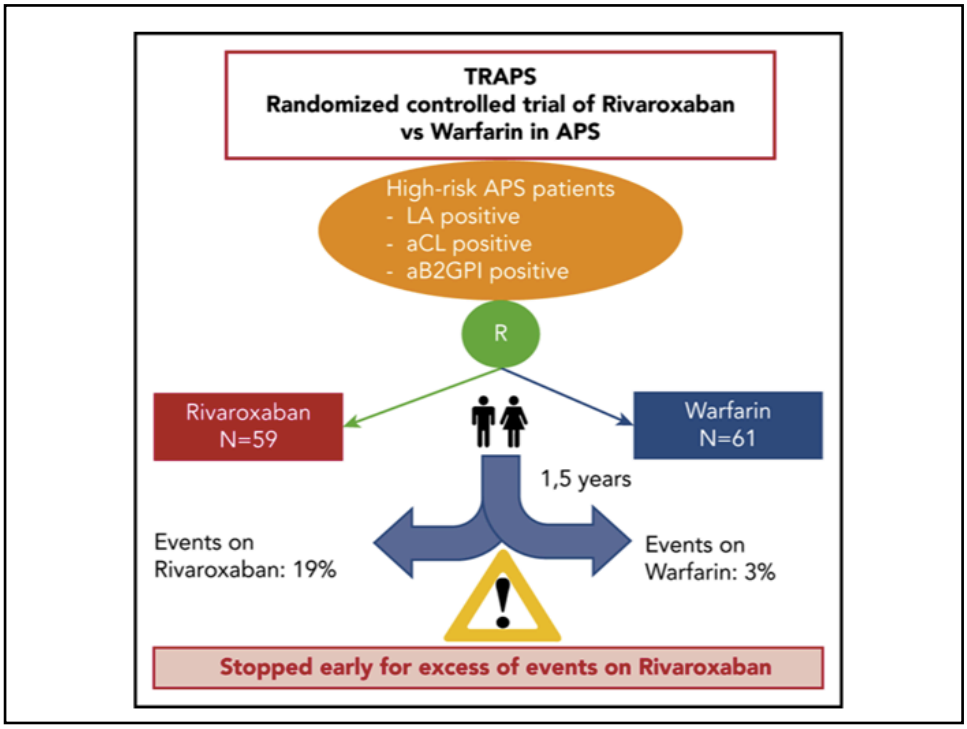
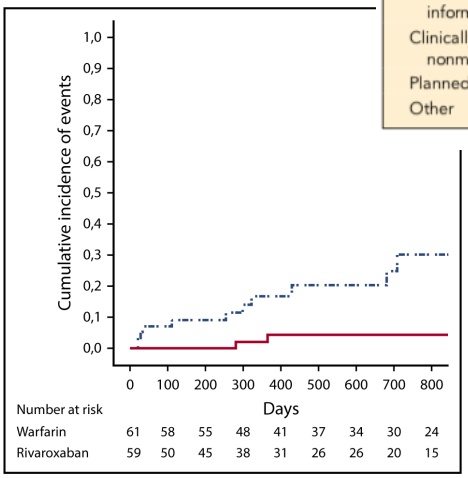


Table 2. Reasons for rivaroxaban or warfarin discontinuation during the study period

	Rivaroxaban	Warfarin
Discontinuation, n, (%)	9 (15)	3 (5)
Withdrawal of informed consent	2	1
Clinically relevant nonmajor bleeding	2	0
Planned pregnancy	3	1
Other	2	1



Pengo Blood, 2018

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Numbers in parentheses denote percentage with respect to total

Unexpected? DOAC were meant for prevention of VTE

> Blood Adv. 2021 Oct 18;bloodadvances.2021005808. doi: 10.1182/bloodadvances.2021005808. Online ahead of print.

Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial

Scott C Woller [1], Scott M Stevens [1], David Kaplan [2], Tzu-Fei Wang [3], D Ware Branch [4], Danielle Groat [5], Emily L Wilson [6], Brent Armbruster [5], Valerie T Aston [5], James F Lloyd [6], Matthew T Rondina [7], C Gregory Elliott [1]

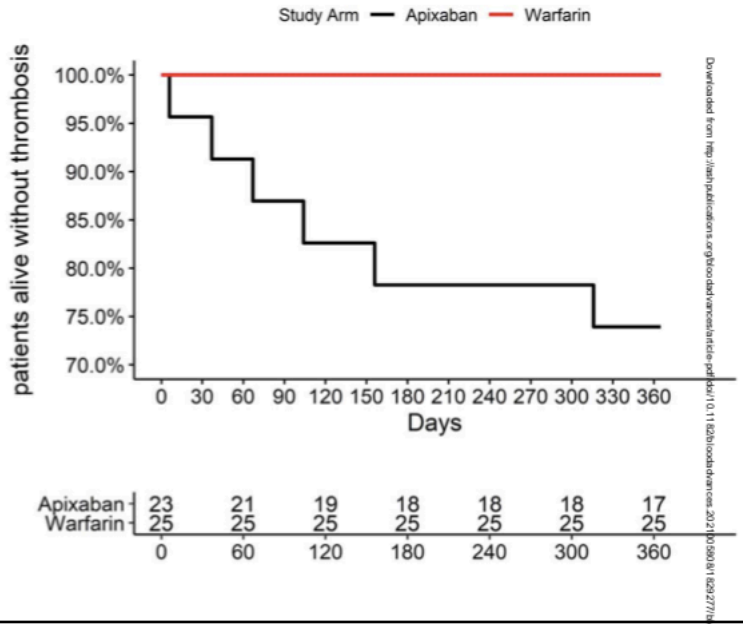
Affiliations + expand

PMID: 34662890 DOI: 10.1182/bloodadvances.2021005808

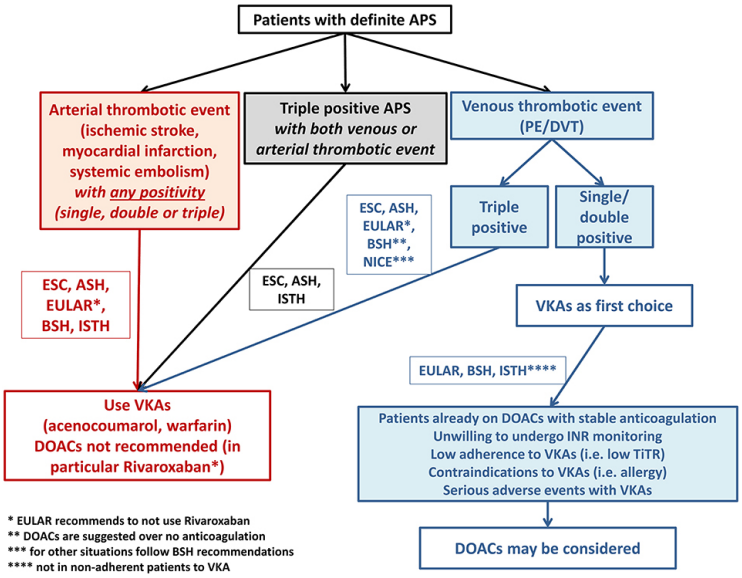
Abstract

Thrombotic antiphospholipid syndrome (TAPS) is characterized by venous, arterial, or microvascular thrombosis. Patients with TAPS merit indefinite anticoagulation and warfarin has historically been the standard treatment. Apixaban is an oral factor Xa inhibitor anticoagulant that requires no dose adjustment or monitoring. The efficacy and safety of apixaban compared with warfarin for TAPS patients remain unknown. This multicenter prospective randomized open-label blinded endpoint study assigned anticoagulated TAPS patients to apixaban or warfarin (target INR 2-3) for 12 months. The primary efficacy outcome was clinically overt thrombosis and vascular death. Apixaban was first given at 2.5 mg twice daily. Two protocol changes were instituted based on recommendations from the data safety monitoring board. After the 25th patient was

› Blood Adv. 2021 Oct 18;bloodadvances.2021005808. doi: 10.1182/bloodadvances.2021005808.
Online ahead of print.



Is this the end for DOAC in APS



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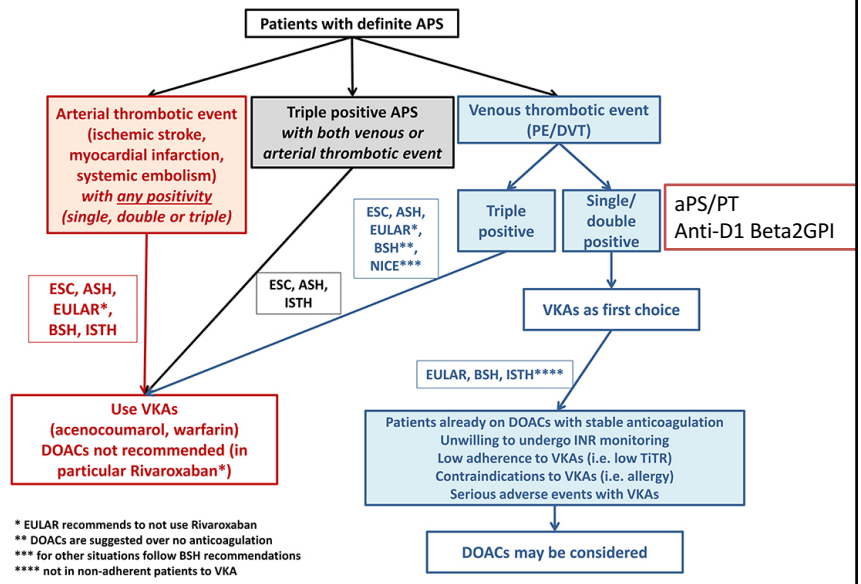

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Hydroxychloroquine and aPL/APS

- In studies in animal models and human aortic endothelial cells, improves procoagulant status and vascular function in APS by modulating endothelial nitric oxide synthase (eNOS), leading to an improvement in the production of NO
- reduces the risk of thrombosis in SLE patients and APS animal models
- reduces aPL levels and arterial thrombosis recurrence in primary APS patients.

Miranda S PloS one. 2019
Belizna C. Autoimmun Rev. 2015
Nuri E Immunol Res. 2017

Hydroxychloroquine and aPL/APS for who?

- In aPL carriers (as primary thrombosis prevention of persistently aPL-positive but thrombosis free patients with no other systemic auto immune diseases)
  --> PROBABLE BUT HARD TO PROVE

Ekan D Lupus 2018

- In APS patients as secondary thromboprophylaxis
  --> CONSIDERED in REFRACTORY CASES

Cohen H Blood 2021

- To reduce the risk of aPL-related pregnancy morbidity?

Observational cohort study of 170 pregnancies in 96 women with aPL

	HCQ group N = 51	Control group N = 119	
Live birth rate	66.7%	57.1%	p=0.05
Overall pregnancy morbidity	47.1%	63.0%	p=0.004
Fetal losses > 10 weeks	2%	10.9%	p=0.05
Ischemic placenta mediated complications	2%	10.9%	p=0.05
Pregnancy duration	27.6 [6-40]	21.5 [6-40]	p=0.03
Live births before 37 weeks	3.9%	13.4%	p=0.05

Sciascia et al, AMOG, 2015

Current ongoing studies on HCQ in OAPS

- **HIBISCUS study** Hydroxychloroquine for the secondary prevention of thrombotic and obstetrical events in primary antiphospholipid syndrome – *set up phase*

  Belizna et al. Autoimmunity Reviews 2018

- **BBQ study:** Hydroxychloroquine for prevention of recurrent miscarriage: study protocol for a multicentre randomised placebo-controlled trial – *recruitment phase*

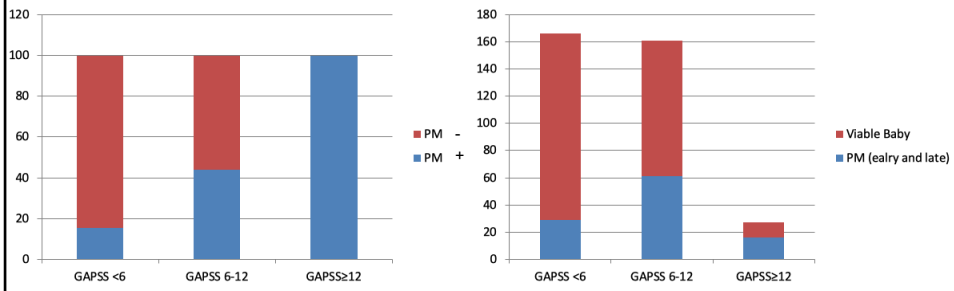
  Pasquier et al. BMJ Open 2019

- **HYPATIA study** (HYdroxychloroquine to Improve Pregnancy Outcome in Women with AnTIphospholipid Antibodies) (EudraCT 2016-002256-25) – *recruitment phase*

  Schreiber et al. Seminars Thromb Haem 2017

Scoring systems impacting on management

- 143 women ever pregnant treated with SoC therapy with SLE and aPL+
- Treated with Standard of Care (SoC) with low dose aspirin (75–100mg/day) and/or low molecular heparin or unfractionated heparin
- GAPSS calculated for each of them and pregnancy prospectively followed.



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IVIG in APS for who?

Useful if concomitant thrombocytopenia refractory to rituximab

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Heterogeneity in schemes used

Refractory cases?

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Intravenous immunoglobulins and antiphospholipid syndrome: How, when and why? A review of the literature

Sara Tenti, Sara Cheleschi, Giacomo Maria Guidelli, Mauro Galeazzi, Antonella Fioravanti *

Rheumatology Unit, Policlinico "Le Scotte", Department of Medicine, Surgery and Neurosciences, University of Siena, Italy

IVIG in APS for who?

Useful if concomitant thrombocytopenia refractory to rituximab

Cohen H Blood 2021

Heterogeneity in schemes used

Refractory cases?

Table 5
Original articles or case reports that report the efficacy of IVIG in preventing thrombosis relapses in APS patients.

References	Trial design	N° of pts	N° of previous thrombotic events	Autoantibodies profile	Treatment to reduce recurrence of thrombosis	Main findings
Hsiao et al. 2001	Case report	1	3 (2 of these under anticoagulation)	aCL IgG and IgA	IVIG (200 mg/kg over 5 days, then 40 mg/kg/month) + warfarin + aspirin (325 mg/day)	IgG and IgA aCL levels decreased after IVIG infusion and no further episodes of thrombosis occurred
Arabshahi et al. 2007	Case report	1	1 (cerebral thrombosis)	aCL IgG	IVIG (2 g/kg/month for 2 year and then every other month for 7 year) Contraindication to warfarin	aCL were no longer detectable within 6 months and continued to be negative. There was no clinical deterioration or further changes on MRA over 7 years
References	Trial design	N° of pts	N° of pts with previous thrombotic events	Autoantibodies profile	Treatment to reduce recurrence of thrombosis	Main findings
Sciascia et al. 2012	Open prospective	5	5/5 (total no of events = 9)	aCL, antiβ2GPI and LA	All pts: IVIG (400 mg/kg for 3 days every month for 3 months, followed by 400 mg/kg/month for 9 months) + oral anticoagulant + HCQ. 3 pts also ASA	In a long-term follow-up (>5 years) no further thrombosis occurred in all pts. VAS score improved after IVIG treatment
Tenti et al. 2013	Open-label prospective comparative	14 Group I: 7 pts Group II: 7 pts	Group I: 7/7 (total no of events = 9) Group II: 7/7 (total no of events = 8)	Group I and II: LA and aCL IgG (7 pts); aCL IgM (2 pts); antiβ2GPI IgG (6 pts); group I: antiβ2GPI IgM (4 pts) Group II: antiβ2GPI IgM (3 pts)	Group I. 7 pts: IVIG (400 mg/kg/month for 2 years) + warfarin (3 pts), ASA (2 pts), warfarin + ASA (2 pts) Group II: warfarin (4 pts), warfarin + ASA (1 pt), acenocumarol (2 pts)	Group I: no venous or arterial thrombosis occurred during the follow-up (2 years); at the end of the study, aCL and antiβ2GPI IgM significantly decreased. Group II: 2 pts presented cerebral ischaemic attacks and one pt a DVT during the follow-up

Abbreviations: pts = patients; aCL = anticardiolipin antibodies; IVIG = intravenous immunoglobulins; MRA = magnetic resonance arteriography; β2GPI = beta-2 glycoprotein 1; LA = lupus anticoagulant; HCQ = hydroxychloroquine; ASA = acetylsalicylic acid; VAS = visual analogue score; DVT = deep vein thrombosis.

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ECULIZUMAB AND LN

Study	Year	Renal biopsy characteristics	IF on renal biopsy	aPL	Indication	Response	F/U
Hadaya et al	2011	LN with TMA lesions; diffuse glomerular and arteriolar TMA with complement deposition in kidney graft. Repeated kidney graft biopsy revealed complete resolution of TMA without sequel.	C4d: negative; moderate staining for C3 and C5b-9 along and within the arterial walls.	LA, aCL, and anti-b2GPI antibodies: positive.	Recurrent TMA after renal transplantation in a patient with SLE-related APS with renal involvement	Yes	6 months
Coppo et al	2014	Class IV-G diffuse proliferative LN. No microangiopathic lesions detected in either of the two renal biopsies performed.	Subendothelial and mesangial deposits (IgG +++,IgM +++, IgGA++, C1q ++, C3 +++, C4 +)	LA, aCL, and anti-b2GPI antibodies: negative.	aHUS in a patient with LN refractory to other immunosoppressive therapies	Yes	17 months
El-Husseini et al	2014	First biopsy: Class V LN. Repeat kidney biopsy:class III and V LN with cellular crescents and mesangiolysis. TMA features (arteriolar fibrin thrombi and fibrinoid necrosis)	Full-house staining in the mesangium and capillary loops	LA, and aCL: negative	LN complicated by TMA refractory to standard therapy	Yes	6 months
Kronbichler et al	2014	TMA lesions	C1q+++; IgM+++, C3+, IgG+, and IgA+.	aCL, anti-b2GPI antibodies: positive	Catastrophic APS (biopsy proven TMA in SLE)	Yes	12 months
Pickering et al	2015	Class IV-G LN with acute tubular damage with foci of lymphocytic tubulitis and marked chronic inflammatory interstitial infiltrate	Mesangial and capillary wall staining positive for C9 at	N/A	Severe resistant LN	Yes	18 months
Boneparth et al	2015	Diffuse proliferative lupus nephritis	N/A	N/A	SLE-related TTP	Y	3W

Sciascia S Roccatello D at al. Rheumatol Int. 2017

ECULIZUMAB AND APS

Table 2
Manifestations of thrombotic microangiopathy and failed therapies

Patient ID	1	2	3	4	5	6	7	8	9
Organ involvement[a]	Renal, hematologic	Bone infarcts, hematologic	Renal, hematologic	Renal, cardiac, hematologic, skin	Renal, hematologic	Renal, pulmonary, hematologic	VTE, Hematologic, neurological	Renal, hematologic	Renal, hematologic
Platelets (K/uL)	92	22	45	88	34	58	45	68	53
Hemoglobin (g/dL)	7.1	7.3	14.0	7.1	6.8	8.9	9.4	7.4	6.9
Lactate dehydrogenase (U/L)	490	216	765	450	484	967	262	367	726
Hypocomplementemia	+	+	–	+	+	+	–	+	+
C3 (mg/dL)	43	47	83	42	22	39	90	24	51
C4 (mg/dL)	7	13	25	6	6	7.5	29	4	16
Creatinine (mg/dL)	1.44	NA	4.31	4.23	1.4	2	NA	1.57	4.75
eGFR (mL/min/1.73m2)	51	NA	14	15	54	33	NA	52	10
Renal failure requiring hemodialysis	–	NA	+	+	–	–	NA	–	+
Renal biopsy	LN Class IV[b]	NA	TMA	TMA	TMA, LN Class IV + V	TMA, LN Class IV	NA	TMA, LN Class IV	LN Class IV + V[b]
ADAMTS13 activity (%)	NAV	NAV	59	54	58	56	NAV	69	67
Failed therapies	Pulse-dosed steroids, CYC	High-dose steroids, anticoagulation	Pulse-dosed steroids, anticoagulation, PEX	Pulse-dosed steroids, anticoagulation, PEX	Pulse-dosed steroids, PEX, MMF	Pulse-dosed steroids, PEX, anticoagulation, CYC	Anticoagulation, pulse-dosed steroids, PEX, RTX, CYC	Pulse-dosed steroids, PEX, RTX	Pulse-dosed steroids, PEX, CYC
Sessions of plasma exchange	NA	NA	7	4	5	6	NAV	4	3
Duration from TMA onset to initiation of eculizumab (days)	27	+/- 180 days	16	14	21	24	+/- 180 days	21	18

Kello Arthritis Rheum 2019

ECULIZUMAB AND APS

Improvement in platelet count at 4 weeks (%)	100%
>25%	100%
>50%	89%
>75%	78%
Normalization of platelet count at any time point	67%
Resolution of hemolytic anemia at 4 weeks	67%
Increase in GFR by 25% at 4 weeks	50%
Increase in GFR by 25% at 12 weeks	50%
Decrease in urine protein:creatinine ratio at 4 weeks	43%
Survival at 3 months	100%
TMA event-free status during eculizumab	100%

-May be beneficial in APS-related refractory microvascular thrombotic states, including thrombotic microangiopathy or chronic persistent microvascular thrombosis

-Good efficacy on PLTs

-Novel anti-Complement T?

Kello Arthritis Rheum 2019

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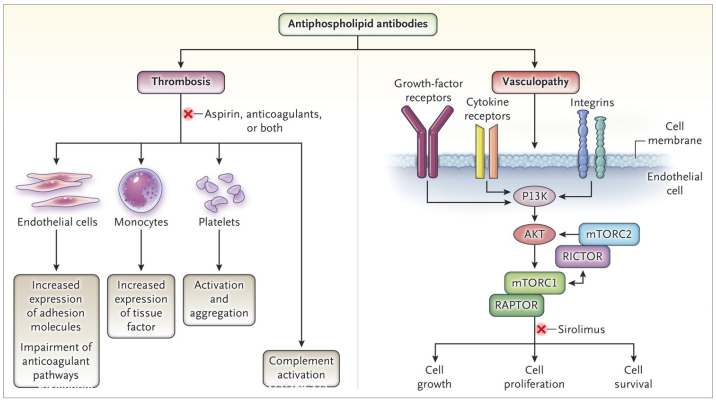
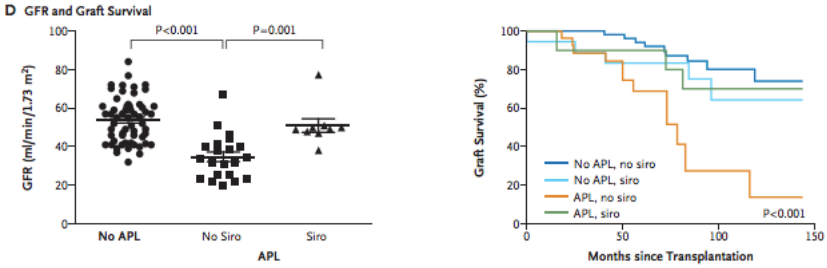
PATHOGENESIS OF THROMBOSIS AND VASCULOPATHY IN APS



Canaud NEJM 2014

PATHOGENESIS OF THROMBOSIS AND VASCULOPATHY IN APS



Probability of graft survival in each group of transplant recipients.

Of the 74 recipients without APL, 56 did not receive sirolimus and 18 did; of the 37 recipients with APL, 27 did not receive sirolimus and 10 did. P

Canaud NEJM 2014

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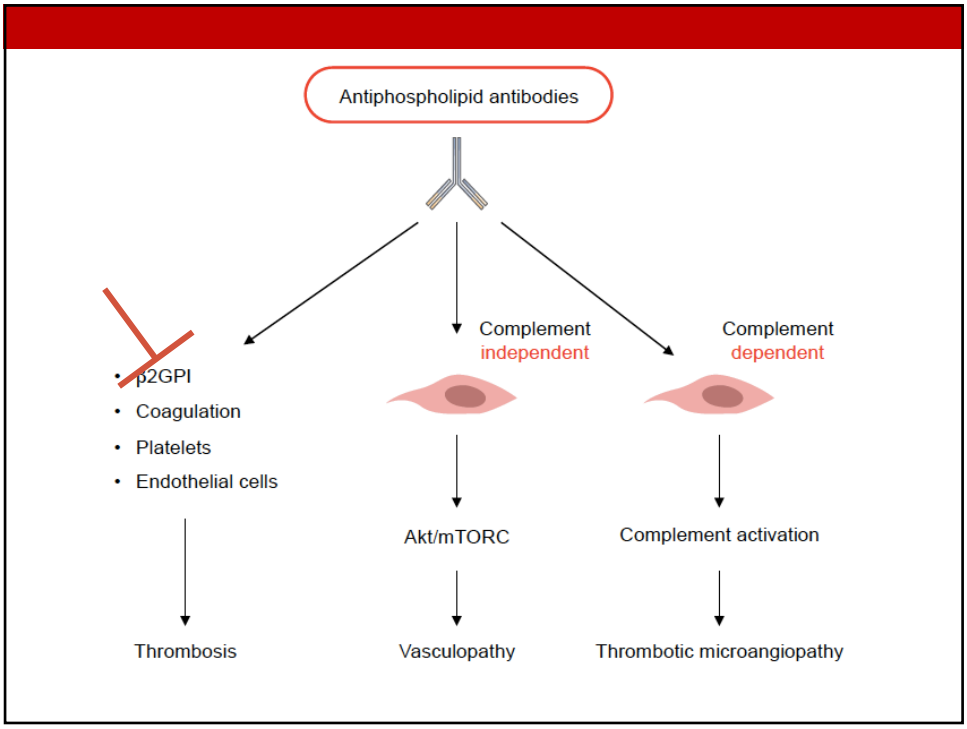
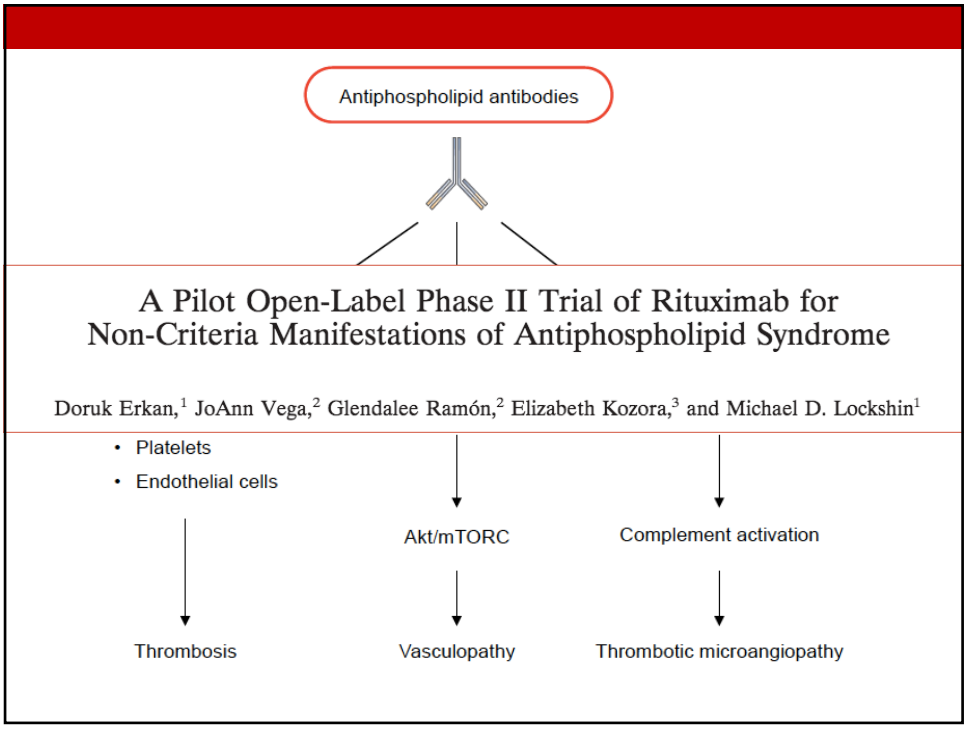

Antiphospholipid antibodies
Complement independent
Complement dependent
β2GPI
Coagulation
Platelets
Endothelial cells
Akt/mTORC
Complement activation
Thrombosis
Vasculopathy
Thrombotic microangiopathy


Antiphospholipid antibodies
A Pilot Open-Label Phase II Trial of Rituximab for Non-Criteria Manifestations of Antiphospholipid Syndrome
Doruk Erkan,[1] JoAnn Vega,[2] Glendalee Ramón,[2] Elizabeth Kozora,[3] and Michael D. Lockshin[1]
Platelets
Endothelial cells
Akt/mTORC
Complement activation
Thrombosis
Vasculopathy
Thrombotic microangiopathy

Rituximab and APS

Patient/ age/sex	APS	Inclusion criteria/duration	Previous medications†	Concomitant medications‡	Response at 24 wks	Observations at 24–52 wks§	Observations after 52 wks (duration from study completion to time of report)¶
1/61/M	No	Skin ulcer (PG)/36 mos	CS, WAR, LMWH, AZA	ASA, PTX, HCQ, MMF	RC	Active ulcers	–
2/25/M	No	Cardiac valve disease/3 mos	–	–	NR	–	No change (6 mos)
3/32/M	No	Thrombocytopenia/3 mos	–	ASA, HCQ	ET	–	–
		Cardiac valve disease/1 wk			ET	–	–
		Cognitive dysfunction/48 mos#		–	ET	–	–
4/40/F	No	Thrombocytopenia/6 mos	CS, IVIG, WinRho	–	CR	No change	Recurrence (4 mos)
5/38/F	PM	Thrombocytopenia/8 mos	CS, IVIG	ASA, HCQ	PR	No change	–
		Cognitive dysfunction/24 mos#			CR	–	–
6/24/F	VE	Thrombocytopenia/5 mos	CS, WinRho	WAR	NR	–	–
7/61/F	No	Cognitive dysfunction/6 mos#	–	ASA, HCQ, STN	CR	–	–
8/53/M	No	Cognitive dysfunction/10 mos#	–	WAR, HCQ, MMF	PR	–	–
9/46/F	VE + PM	Cognitive dysfunction/12 mos#	CS	ASA, WAR	CR	–	–
10/20/F	VE	Skin ulcer (LV)/2 mos	CS	HCQ, STN, WAR	CR	No change	–
11/45/M	VE	Skin ulcer (PG)/5 mos	CS, IVIG	WAR	CR**	Active ulcers	–
12/46/F	VE + PM	Thrombocytopenia/12 yrs	CS, TPO	HCQ, CPG, WAR	ET††		
		Cardiac valve disease/3 mos			ET	–	–
13/52/M	VE	Cardiac valve disease/1 mo	–	STN, WAR	NR	–	Improved (17 mos)‡‡
14/38/M	VE	Skin ulcer (PG)/1.5 mos	–	HCQ, WAR	CR	No change	–
15/22/M	No	aPL nephropathy/2 mos	CS	ACE inhibitor	ET	–	–
16/61/F	VE	Skin ulcer (PG)/22 mos	CS	ASA, STN	PR	Recovered	–
17/20/F	No	aPL nephropathy/35 mos	CS, MMF	ACE	PR	No change	–
18/45/F	PM	Cognitive dysfunction/3 mos#	–	ASA, HCQ	NR	–	–
19/41/F	PM	Cardiac valve disease/25 mos	–	ASA	NR	–	Improved (5 mos)§§

Erkan AR 2014

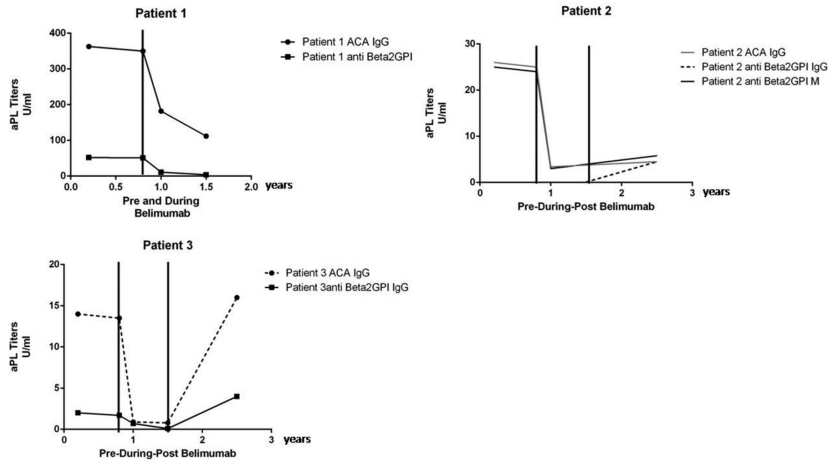
Rituximab and APS

	OUTCOMES at 24 months			
	CR	PR	NR	Recurrence
Thrombocytopenia	1	1	2	0
Cardiac valve disease	0	0	3	N/A
Skin ulcer	3	1	0	1
aPL nephropathy	0	1	0	0
Cognitive dysfunction	3	1	1	N/A



Erkan AR 2014

aPL titres of the three patients in relationship with belimumab therapy. aPL, antiphospholipid antibodies.



Sciascia et al. Ann Rheum Dis 2018

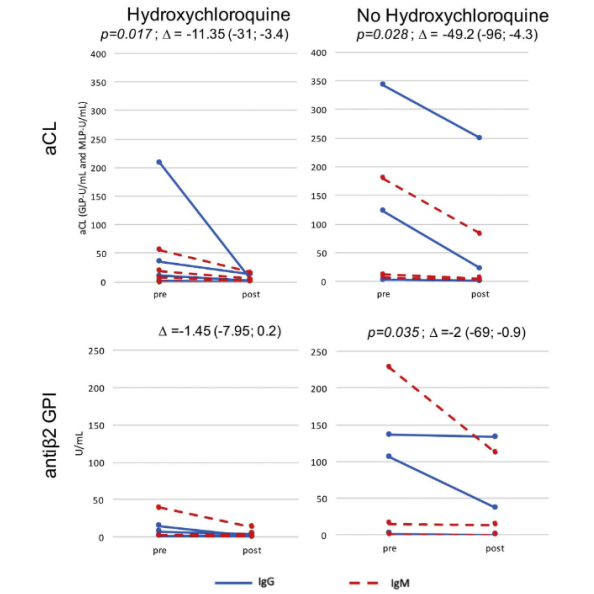
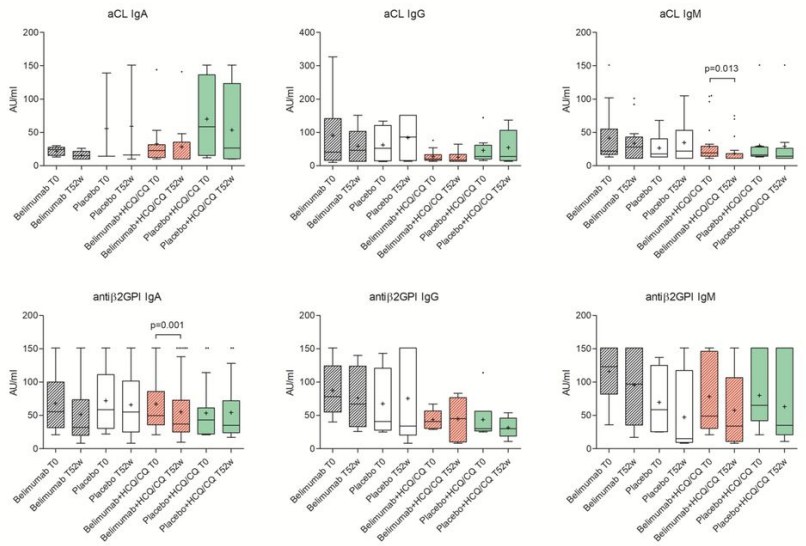


Fig. 1. Variations in the levels of anti-cardiolipin (aCL) and anti-beta2 glycoprotein I (antiβ2 GPI) IgG and IgM antibodies, before vs after treatment with belimumab in patients treated or never treated with hydroxychloroquine.

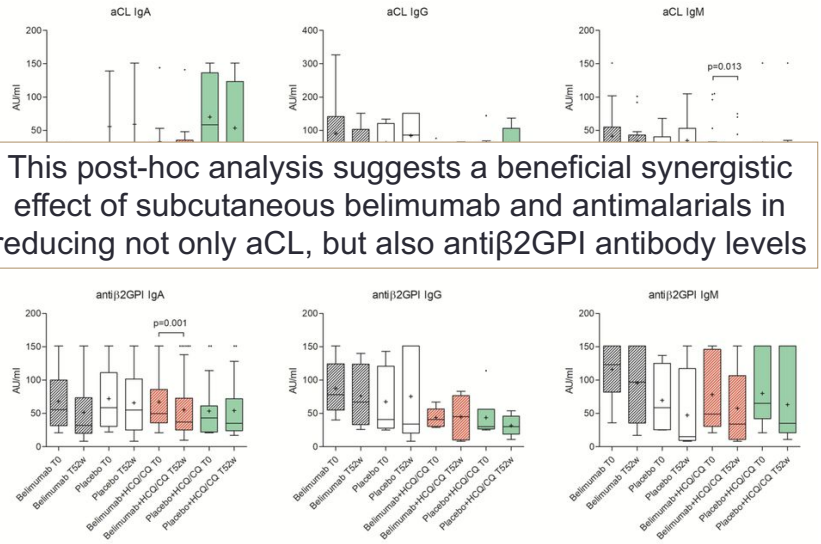
Emmi G et al. Aut Rev 2019

b)



Bettiol et al. Ann Rheum Dis 2020

b)



This post-hoc analysis suggests a beneficial synergistic effect of subcutaneous belimumab and antimalarials in reducing not only aCL, but also antiβ2GPI antibody levels

Bettiol et al. Ann Rheum Dis 2020

Belimumab reduces antiphospholipid antibodies in primary triple-positive antiphospholipid syndrome.

→ fluctuating INR could be stabilized, and affection of the heart valve disappeared.

aPl.	Pre belimumab	after 6 months of belimumab
aCL IgG [U/ml] (norm value 0–20)	2024	560
aβ2GPI IgG [U/ml] (norm value 0–20)	6100	1637
LA [RVV-ratio] (norm value 0–1.4)	1,94	1,49
aCL IgM [U/ml] (norm value 0–20)	4,6	2,6
aβ2GPI IgM [U/ml] (norm value 0–20)	2,5	0,7

aCL: antibodies against cardiolipin; aβ2GPI: β2 glycoprotein I; LA: lupus anticoagulant; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

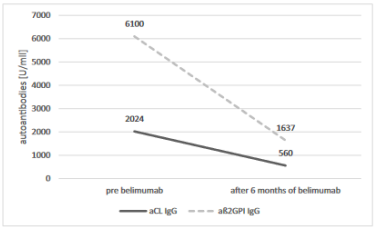
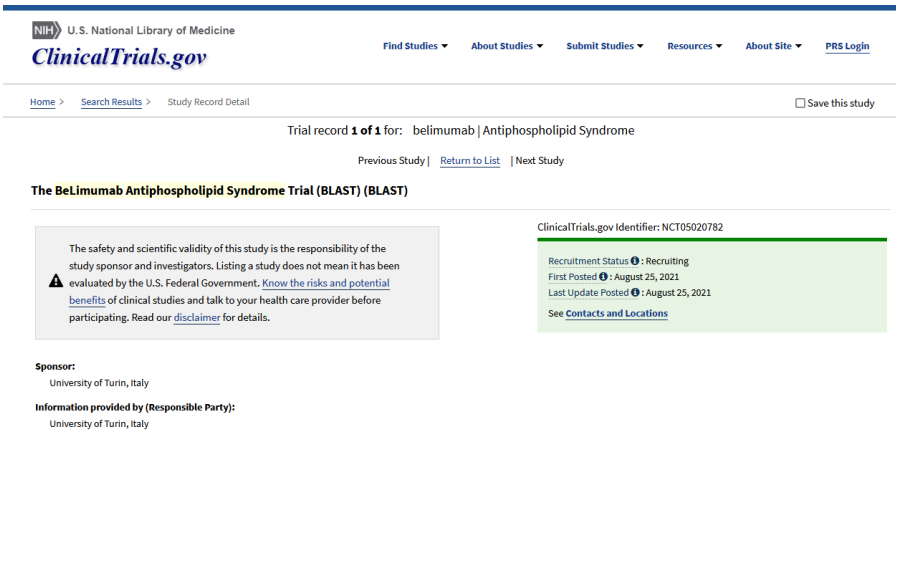
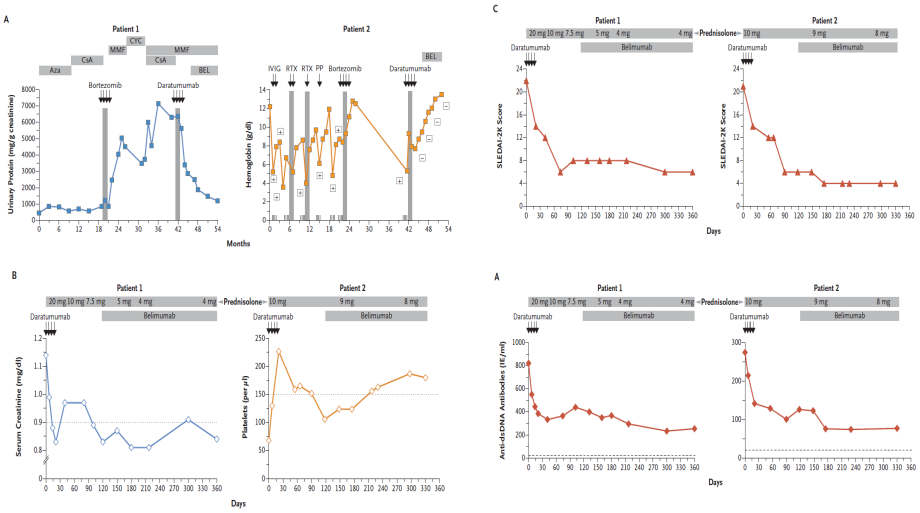


Fig. 1. aPl. before and during belimumab therapy.
aCL: antibodies against cardiolipin; aβ2GPI: β2 glycoprotein.

Klemm P, Autoimmun Rev . 2020



Targeting CD38 with Daratumumab in Refractory Systemic Lupus Erythematosus



Ostendorf , N Engl J Med, 2020

frontiers in Immunology

Front Immunol. 2021; 12: 667515.
Published online 2021 Apr 12. doi: 10.3389/fimmu.2021.667515

PMCID: PMC8072150
PMID: 33912194

Case Report: Resetting the Humoral Immune Response by Targeting Plasma Cells With Daratumumab in Anti-Phospholipid Syndrome

Daniel E. Pleguezuelo, [1,*] Raquel Díaz-Simón, [2] Oscar Cabrera-Marante, [1] Antonio Lalueza, [2] Estela Paz-Artal, [1] Carlos Lumbreras, [2] and Antonio Serrano Hernández [1]

-APS case treated with daratumumab, an anti-CD38 mAb, in a 21-year-old patient with APS who presented with recurrent venous thromboembolic events despite adequate anticoagulant therapy.

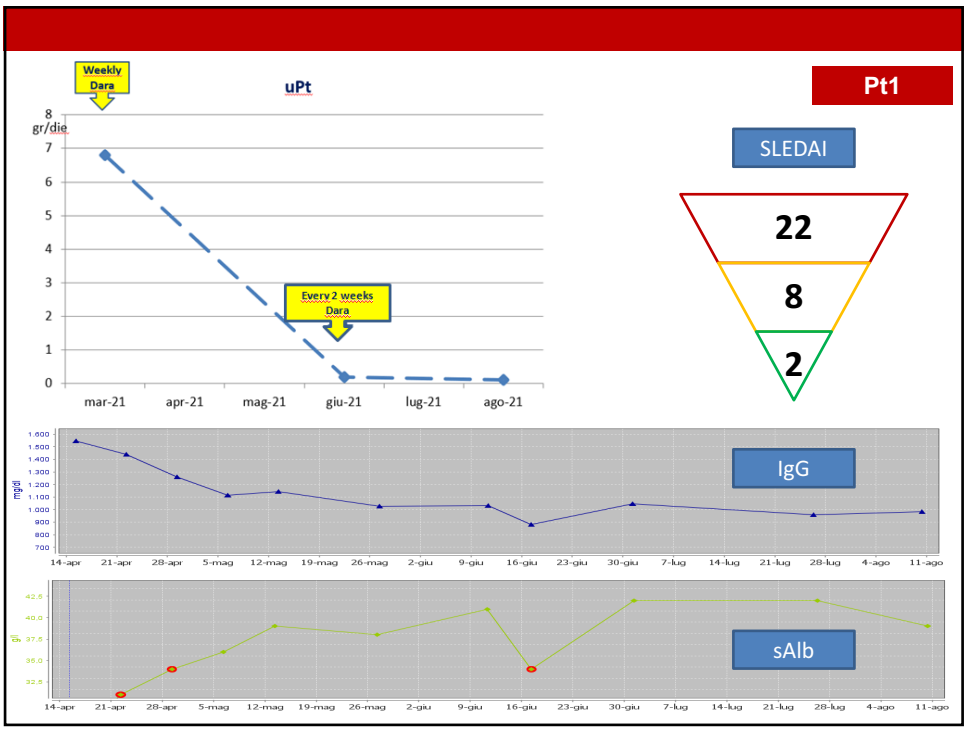
-She was administered one dose weekly of daratumumab for 4 weeks. The treatment showed an adequate safety profile and was well tolerated.

-the therapy, her levels of positive aPL declined significantly and most continued to decrease during the next three months.

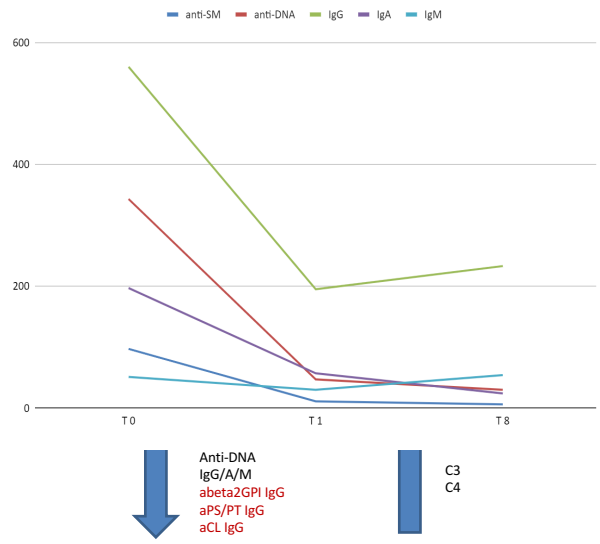
Patients currently being treated with Daratumumab

	Age (yrs)	Previous treatment	LN Class	Follow-up Dara (months)
Pt1	24	GC-MMF-RTX+CYC-	v	9
Pt2	39	GC-RTX+CYC-Bel-CYC-AZA	IV+V	5
P43	60	GC-RTX (9 Cycles)	III+V	< 3
Pt4	54	GC-MMF-ivIg-Bel	IV	< 3
Pt5	20	MMF – RTX+CYC - Bel	III-V	< 3

Infusions 1-8	Infusions 9-16	Infusions 17-24
16 mg/Kg Weekly	16 mg/Kg Every two weeks	16 mg/Kg Monthly



Daratumumab F/U 9 months



Lupus anticoagulant + at T0 turned - at T8

aPL

β2GPI PS/PT Coagulation factors Monocytes PLTs Endothelial cells	→	Thrombois	→ VKA (DOACs?) ASA +Statins +HCQ?
Complement Activation and deposition	→	TMA	→ Eculizumab ? Anti-Complement ?
Akt/mTOR	→	aPL-related Vasculopathy	→ mTOR inihibitors?
Abs production	→	Criteria/ extra criteria manifestations	→ Anti-CD20 Anti-BAFF Anti-CD38?
Immunomodualtion	→	Criteria/ extra criteria manifestations	→ IVIG

Observational Study > Rheumatology (Oxford). 2021 Mar 2;60(3):1106-1113.
doi: 10.1093/rheumatology/kez596.

Identifying phenotypes of patients with antiphospholipid antibodies: results from a cluster analysis in a large cohort of patients

Savino Sciascia [1], Massimo Radin [1 2], Irene Cecchi [1 2], Maria Laura Bertolaccini [3], Maria Tiziana Bertero [4], Elena Rubini [1 2], Antonella Vaccarino [5], Mario Bazzan [5], Osvaldo Giachino [1], Simone Baldovino [1], Daniela Rossi [1], Giulio Mengozzi [6], Dario Roccatello [1]

> Lupus. 2020 Jul 23;961203320940776. doi: 10.1177/0961203320940776. Online ahead of print.

Cluster analysis for the identification of clinical phenotypes among antiphospholipid antibody–positive patients from the APS ACTION Registry

Stéphane Zuily [1 2], Isabelle Clerc-Urmès [3], Cédric Bauman [3], Danieli Andrade [4], Savino Sciascia [5], Vittorio Pengo [6], Maria G Tektonidou [7], Amaia Ugarte [8], Maria Gerosa [9], H Michael Belmont [10],

Different risk in different sub-setting