Anticoagulation in patients with concomitant lupus nephritis and thrombotic microangiopathy: A multicentre cohort study

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Running headline: anticoagulation in LN and TMA

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The management of lupus nephritis (LN) and concomitant thrombotic microangiopathy (TMA), with or without antiphospholipid antibodies (aPL), remains controversial and few studies are available to inform clinical management [1–4]

The purpose of this multicenter retrospective study was to analyze the impact of anticoagulation [vitamin-K-antagonists (VKA) and/or heparins] in addition to conventional immunosuppression on kidney outcomes (assessed at 12 months, according to KDIGO guidelines[5]) in patients with biopsy-proven LN and concomitant TMA.

Data source, population, and statistical analysis are detailed in the supplementary material. Anticoagulation was considered if given for at least 3 consecutive months after TMA diagnosis.

We retrospectively identified 97 patients with biopsy-proven LN and TMA (2007-2017). See online supplementary Table S1 for clinical and demographic characteristics. Laboratory parameters were collected at the time of the biopsy. The mean age of patients was 38.9 ±15.2 years (13–69) and 85 female (87.6%). Most had proliferative LN (Class IV in 84.5%). Forty-two(43%) patients presented with acute and 55 (57%) with features of chronic TMA. All patients had received treatment with standard immunosuppressants (55% mycophenolate, 39% cyclophosphamide, 6% other regimen) and steroids. At 12 months, complete response (CR) was observed in 37 patients (38.1%), partial response (PR) in 22 (22.6%) and no response in 38 (39.1%). Sixty-one patients (62.9%) were aPL positive and 37 (38.1%) of these patients received anticoagulation with a VKA and/or heparins. Mean duration of anticoagulation therapy after TMA and LN diagnosis was 7.7 months (3-12).

We observed a higher rate of clinical response (CR/PR, together or computed separately) in patients who received anticoagulation [CR in 22 (59.46%), PR in 7 (18.91%); NR in 8 (21.62%)] when compared to those without [CR in 15 (25.0%), PR in 15 (25.0%); NR in 30(50%)], p<0.01) (Table1).

When limiting the analysis on the 61 patients with aPL, we observed a higher rate of complete response in those receiving anticoagulation [patients receiving anticoagulant therapy: CR in 22 (59.46%), PR in 7 (18.91%); NR in 8 (21.62%) Vs. patients non receiving VKA/heparins: CR in 8 (30.77%), PR in 7 (26.92%); NR in 8 (34.62%),p=0.046](Figure 1).

After multivariate analysis, aPL positivity (any) (β=1.23,OR, 2.4;95% confidence interval-CI-, 1.2–7.3;p=0.03), anti-dsDNA positivity (β=1.98,OR,12.8; 95% CI 3.0-71.3; p=0.002), and chronic features of TMA (β=1.31,OR 3.0; 95%CI 1.2–17.5; p =0.04) were all associated with no kidney response.

When limiting the analysis to aPL positive patients, after adjusting for type of immunosuppressant therapy and LN class, variables that were significantly associated with CR+PR were features of acute TMA rather than chronic (β=1.95, OR, 8.62; 95% CI 1.4–97.1; p = 0.03) and the use of VKA/heparins (β=1.21OR, 2.1; 95% CI, 1.02–16.2; P = 0.046).

In summary, in our study the use of anticoagulation was associated with any response to treatment at 1 year, in line with the fact that about 60% of the patients with CR received VKA or heparins. Similarly, when limiting the analysis to patients with aPL, we observed a rate of any response (either CR+PR) as high as 66% in patients receiving anti-coagulant treatment when compared to those receiving immunosuppression alone (34%).

Despite its limitations (the relatively short duration of follow-up to gauge the relapse rate; lack of standardized protocol for LN treatment; the use of anticoagulation agents was not randomized but based on the treating physicians' judgment), this study represents the largest available multicentre cohort of real-life SLE patients with biopsy proven LN and concomitant TMA.

To conclude, in patients with concomitant LN and TMA, the use of anticoagulation appeared protective and warrants further investigation as a therapeutic tool; the presence of aPL, anti-dsDNA antibodies and chronic features of TMA were associated with poorer kidney outcomes.

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Manuscripts based on work previously presented at the following conferences and published as a conference abstract.

ACR 2018: https://acrabstracts.org/abstract/clinical-outcomes-and-response-to-anti-thrombotic-treatment-among-patients-with-concomitant-lupus-nephritis-and-thrombotic-microangiopathy-a-multicenter-cohort-study/?msg=fail&shared=email

EULAR 2018: https://web.eular.org/EULAR_Production/2018_Amsterdam.nsf/fmWebPGMbyDayPublic?OpenForm

Legends:

Figure 1

Comparison of kidney outcomes between patients receiving anticoagulation and those without (Panel A, all 97 patients; Panel B, limiting to patients positive for antiphospholipid antibodies)

Table 1. Univariate analysis of patient characteristicsby kidney outcome

Table 1S. Baseline clinical characteristics of patients with TMA and LN

Table 1S

Characteristics		**Total**	**%**
Female		85	87,6
Clinical features			
Skin Involvement		32	33,0
Hematological involvement		35	36,1
Joint involvement		75	77,3
NPSLE		2	2,1
History of hypertension		55	56,7
APS*		13	13,4
Thrombotic APS		10	10,3
Obstetric APS		5	5,2
Clinical features at the time of biopsy			
Microangiopathic hemolytic anemia		3	3,1
Thrombocytopenia (<100,000 platelets/µL)		15	15,5
Laboratory profile			
Anti-Ro positivity		36	37,1
Anti-La positivity		9	9,3
aPL antibody positivity		61	62,9
LAC		37	38,1
aCL		35	36,1
anti-Beta2GPI		22	22,7
Triple Positivity		15	15,5
Anti-dsDNA		43	44,3
Creatinine > 3 mg/dL		27	27,8
low C3 levels		77	79,3
low C4 levels		27	27,8
Microscopic hematuria (>5 erythrocytes/HPF)		69	71,1
Proteinuria > 3.5 mg/d		41	42,3
Arterial hypertension		63	64,9
Hyperlipemia		45	46,3
aGAPPS ≥ 10		29	29,9
aGAPPS ≥ 12		24	24,7
Therapy			
ACE inhibitor or ARB use		62	63,9
Anti-thrombotic therapy			
Aspirin**		54	55,7
Anticoagulation***		38	39,2
Vitamin K antagonist		31	32,0
heparins		7	7,2
Immunosuppressants (Induction therapy for LN)****			
Mycophenolate mofetil		53	54,6
Cyclophosphamide		38	39,2
EUROLUPUS regimen		28	28,9

Other		6	6,2

*according to Sydney criteria (Miyakis et al., 2006); **in 47 patients treatment was initiated before LN diagnosis; *** 10 patients on VKA before LN diagnosis; **** patients received different steroids regimens in association to immunosuppressant agents. The majority of them receive bolus doses of methyl-prednisone followed by 0.8/kg/day of oral prednisone tapered to low-dose (e.g. < 7.5 mg/dl) within 6 months from induction. NPSLE, neuropsychiatric SLE; Miyakis, S., Lockshin, M. D., Atsumi, T., Branch, D. W., Brey, R. L., Cervera, R., … Krilis, S. A. (2006). International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis : JTH, 4(2), 295–306.

Table 1

Characteristics	**Total**	**%**	**Any response**	**%**	**CR**	**%**	**%CR**	**PR**	**%**	**%PR**	**NR**	**%**	**%NR**	**p**	**p***
Female	85	87,6	52	53,6	30	30,9	81,1	22	22,68041	100	33	34,02	86,84	0,2924	0,85
Clinical features															
APS*	13	13,4	10	10,3	5	5,2	13,5	5	5,2	22,7	3	3,1	7,9	0,2629	0,22
aPL antibody positivity	61	62,9	26	26,8	15	15,5	40,5	11	11,3	50,0	35	36,1	92,1	**<0.001**	**<0.001**
LAC	37	38,1	17	17,5	7	7,2	18,9	10	10,3	45,5	20	20,6	52,6	**0,0079**	**0,018**
aCL	35	36,1	20	20,6	8	8,2	21,6	12	12,4	54,5	15	15,5	39,5	**0,0334**	0,57
anti-Beta2GPI	22	22,7	12	12,4	7	7,2	18,9	5	5,2	22,7	10	10,3	26,3	0,7464	0,49
Triple Positivity	15	15,5	8	8,2	5	5,2	13,5	3	3,1	13,6	7	7,2	18,4	0,811	0,51
Anti-dsDNA	43	44,3	22	22,7	13	13,4	35,1	9	9,3	40,9	24	24,7	63,2	**0,041**	**0,0214**
Low C3 levels	77	79,3	36	37,1	25	25,8	67,6	11	11,3	50,0	38	39,2	100,0	**0,001**	**<0.001**
Low C4 levels	27	27,8	15	15,5	8	8,2	21,6	7	7,2	31,8	12	12,4	31,6	0,5627	0,64
Arterial hypertension	63	64,9	36	37,1	23	23,7	62,2	13	13,4	59,1	28	28,9	73,7	0,4252	0,27
Hyperlipemia	45	46,3	27	27,8	17	17,5	45,9	10	10,3	45,5	18	18,6	47,4	0,98	1
aGAPPS ≥ 12	24	24,7	10	10,3	6	6,2	16,2	4	4,1	18,2	14	14,4	36,8	0,0846	**0,0267**
LN class IV	82	84,5	50	51,5	32	33,0	86,5	18	18,6	81,8	32	33,0	84,2	0,8891	1
Therapy															
Mycophenolate mofetil	53	54,6	32	33,0	21	21,6	56,8	11	11,3	50,0	21	21,6	55,3	0,8764	1
Cyclophosphamide	38	39,2	22	22,7	14	14,4	37,8	8	8,2	36,4	16	16,5	42,1	0,888	0,67
EUROLUPUS regimen	28	28,9	16	16,5	11	11,3	29,7	5	5,2	22,7	12	12,4	31,6	0,7583	0,65
Other immunosuppresants	6	6,2	4	4,1	2	2,1	5,4	2	2,1	9,1	2	2,1	5,3	0,8128	1
Anticoagulation	37	38,1	29	29,9	22	22,7	59,5	7	7,2	31,8	8	8,2	21,1	**0,0022**	**0,0059**

*computing together any response, CR+PR. CR, complete response; PR, partial response; NR, no response; aGAPPS, adjusted global antiphospholipid score.