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VIRTUAL CONFERENCE

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Lupus Nephritis Updates to Above and Beyond

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Faculty Disclosures

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- Advisory Board: Amgen, Sanofi, Abbvie

Objectives

- Review the classification of LN
- Review treatment guidelines LN
- Overview of possible new treatment

Lupus Nephritis

- 50-60% of adults and almost 80% of children with SLE develop nephritis within the first 10 years after diagnosis.
- Prevalence is higher in African Americans and Hispanics than in Caucasians, and higher in men than women.
- 88% at 10 years, with African Americans having an even lower survival rate.
- 10-30% of these patients will progress to end-stage renal disease (ESRD).
- The incidence of ESRD caused by SLE has risen for younger African American patients living in the southern United States.

Richey M. The management of lupus nephritis. *Nurse Pract*. 2014 Mar 13;39(3):1-6. doi:10.1097/01.NPR.0000443229.10476.61.PMID: 24535304.

Classification Criteria – ISN/RPS 2003

Classes	Microscopy	Laboratory
Class I – minimal mesangial Class II – mesangial proliferative	Hypercellularity and matrix accumulation result from mesangial immune complex accumulation	Microscopic hematuria and sub nephrotic proteinuria with well-preserved or minimally reduced glomerular filtration rate (GFR).
Class III – Focal LN (<50% of glomeruli) - A, A/C, C Class IV – Diffuse LN (> 50% of glomeruli) Diffuse Segmental (IV-S) or Global (IV-G) A, A/C, C **(Proliferative)**	Leukocyte accumulation, endothelial cell injury, and endocapillary proliferation that is associated with capillary wall destruction, mild to marked immune complex deposition, and crescent formation.	Characterized by acute reduction in GFR, hematuria, and mild to moderated proteinuria
Class V – Membranous LN	Antibodies and complement cause cytotoxic injury resulting in nonexudative, non-proliferative capillary wall lesion (membranous glomerulo-nephropathy)	Significant proteinuria, often with nephrotic syndrome and preservation and/or gradual reduction in GFR
Class VI – Advanced Sclerosing >90% globally sclerosed without residual activity		Renal insufficiency, hematuria and proteinuria

2018 Updates

Table 1. Phase 1 recommendations for lupus nephritis classification		
Category	**Recommendation**	**Comments on ISN/RPS guidelines**
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region (A)	Cutoff for mesangial hypercellularity unclear
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule and should be involved.	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents
	Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C)	
	Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D)	
	Fibrocellular crescent: 25%-75% cells and fibrin and the remainder fibrous matrix (E)	
	Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis (F)	There was no definition for an adhesion
	Fibrinoid necrosis: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis	There was no definition for fibroid necrosis
	Elimination of segmental and global subdivisions of class IV	Definitions for segmental and global were unclear; interobserver variability was large; clinical significance uncertain
	Modification of the NIH lupus nephritis activity and chronicity scoring system (Table 2) and to be used instead of the currently used A, C, and A/C parameters	Designation of activity/chronicity through A, C, and A/C considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis	Lack of cut-off values for reporting the severity of tubulointerstitial lesions

A-F refer to typical examples of glomerular lesions in Figure 1.
Bajema, et al. 2018.

Patterns of Injury

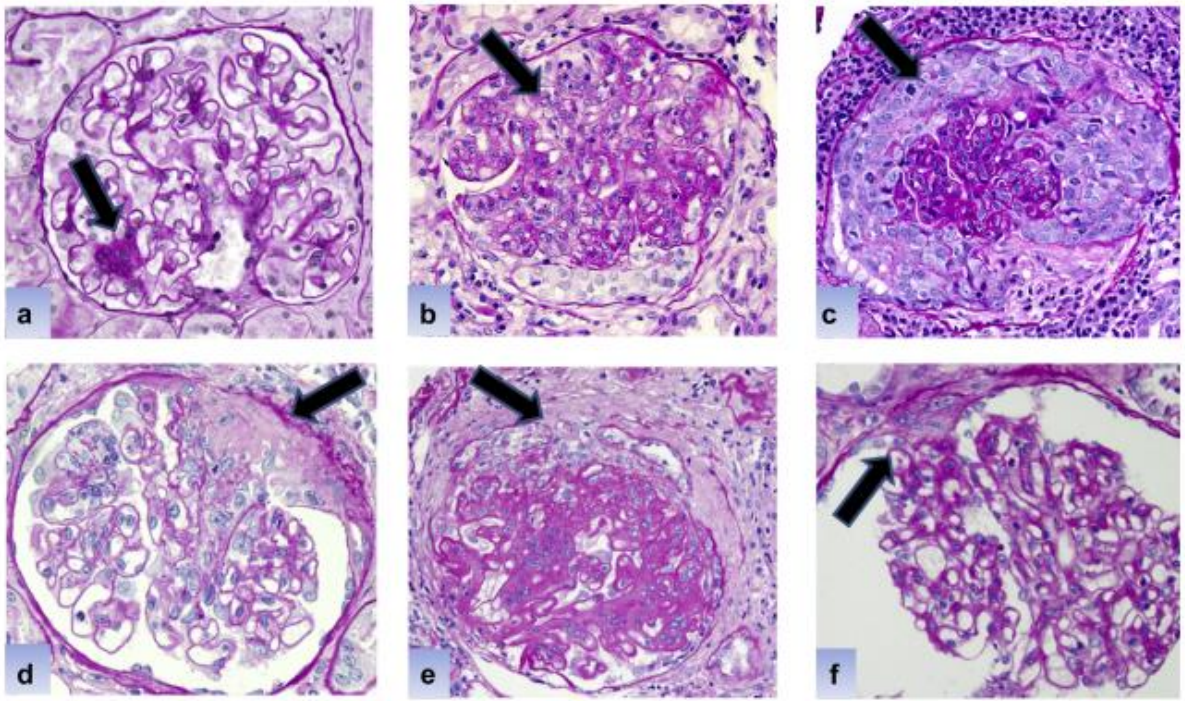

Figure 1. Examples of glomerular lesions for which recommendations were made in Table 1. Arrows point to typical examples. All sections are shown in the PAS staining. (a) Mesangial hypercellularity, (b) endocapillary hypercellularity, (c) cellular crescent, (d) fibrous crescent, (e) fibrocellular crescent, (f) adhesion. PAS, periodic acid-Schiff. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

Patterns of Injury

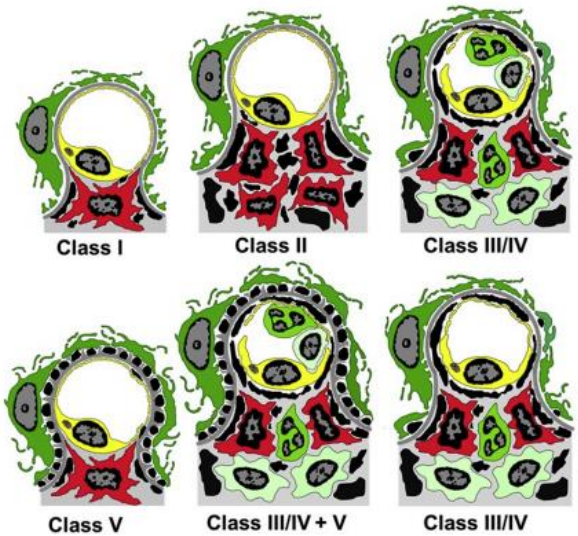

Figure 2. Drawings depicting the ultrastructural features of a single glomerular capillary affected by lupus glomerulonephritis: class I with mesangial immune deposits (black) but no mesangial cell (red) hypercellularity or influx of leukocytes; class II with mesangial immune deposits and mesangial cell hypercellularity but no influx of leukocytes; class III/IV (upper right) with mesangial and capillary influx of leukocytes; class III/IV (lower right) with subendothelial capillary wall immune deposits that can be seen by LM and mesangial but no capillary influx of leukocytes (dark green neutrophils and light green monocytes/macrophages); class III/IV + V with an influx of leukocytes and numerous subepithelial immune deposits in addition to subendothelial deposits; and class V with numerous subepithelial immune deposists but no influx of leukocytes (podocyte = outer green cell, endothelial cell = yellow cell, mesangial cell = red cell, neutrophil = green cell with segmented nucleus, monocyte/macrophage = light green cell). LM, light microscopy.
Bajema, et al. 2018.

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Treatment Overview

ACR 2012 – Treatment Guidelines

Class I (minimal mesangial) and Class II (mesangial proliferative)	Class III (focal) and Class IV (diffuse segmental or global)	Induction therapy for class III and IV	Steroid Use	Cyclophosphamide treatment
• Generally do not require immunosuppressive treatment.	• Aggressive therapy with Glucocorticoids and immunosuppressive agents	• MMF 2-3 gm daily orally or I.V. CYC along with glucocorticoids • Asians may require lower doses of MMF (2 gm daily). • African Americans and Hispanics- MMF is preferred	• Patients will also receive pulse I.V. glucocorticoids : 500-1,000 mg(*****) methylprednisolone daily for 3 doses, followed by daily oral glucocorticoid (0.5-1 mg/kg/day), followed by a taper to the minimal amount necessary to control the disease • *****Current push to decrease steroid dose as per KDIGO10.3.2.1.1	• Euro-Lupus CYC: 500 mg I.V. once every 2 weeks for a total of 6 doses, followed by maintenance therapy with AZA or daily oral MMF (Caucasians). • High dose CYC: 500-1,000 mg I.V. once a month for 6 doses, followed by maintenance treatment with MMF or AZA.

Class V and Combinations

Class V (membranous) combined with class III or IV plus cellular crescents	Class V (membranous) combined with class III or IV	Class V (pure membranous)	Class VI (advanced sclerotic)
• CYC or MMF along with I.V. pulses of high dose glucocorticoid at dose of 1 mg/kg/day	• Should be treated in the same manner as class III/IV	• Glucocorticoids (0.5mg/kg/day) plus MMF 2-3 gm daily	• Preparation for renal replacement therapy (e.g., dialysis)

Proliferative (III and IV) Treatment Options

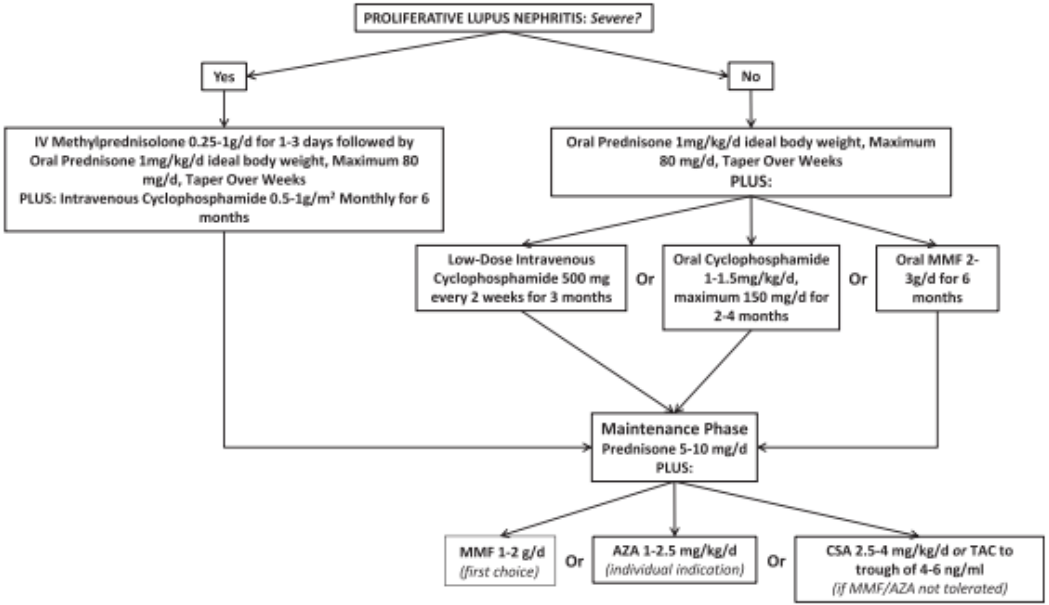

Figure 2. Current induction and maintenance treatment choices for proliferative lupus nephritis. Patients are considered to have severe lupus nephritis if they have functional kidney injury with an elevated serum creatinine and/or heavy proteinuria, evidence that the loss of renal function occurred over a relatively short period of time and active histologic injury with glomerular crescents and necroses affecting several glomeruli.
AZA, azathioprine; CSA, cyclosporine A; MMF, mycophenolate mofetil; TAC, tacrolimus.
Almaani S, Meara A, & Rovin B. H. Update on lupus nephritis. *Clinical Journal of the American Society of Nephrology.* 12(5), 825-835. 2017.

Immunosuppressive Therapy

Mycophenolate	Azathioprine	Cyclophosphamide
Blocks B and T-cell proliferation	Blocks T lymphocytes	Alkylating agent – depletes B and T cells
Started at 500 mg/day with target between 2-3 gms/day for maintenance	• Dose varies from 50 to 150 mg daily • MUST check TPMT enzyme activity before initiation	IV and Oral
• Serious Infections • GI distress • Must use birth control – risk of birth defects • Stop at least 6 weeks before PLANNED PREGNANCY	• GI tract toxicity, oral ulcers, GI distress, Bone marrow suppression • SAFE DURING PREGNANCY	• Common and opportunistic infections • Birth defects, sterility • Hematological malignancy • Hemorrhagic cystitis • Bladder cancer

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Upcoming Treatment

Non-FDA Approved (YET)

- Belimumab (BLISS LN) – Prevent Activation
- Rituximab (LUNAR) – Depletes B cell
- Obinutuzumab (NOBILITY) – Depletes B cell
- Voclosporin (AURORA)

BLISS – LN – Combination Therapy

- 448 patients (224 to the belimumab group and 224 to the placebo group)
- Randomization was stratified according to induction regimen (cyclophosphamide or mycophenolate mofetil) and race group (Black or non-Black)

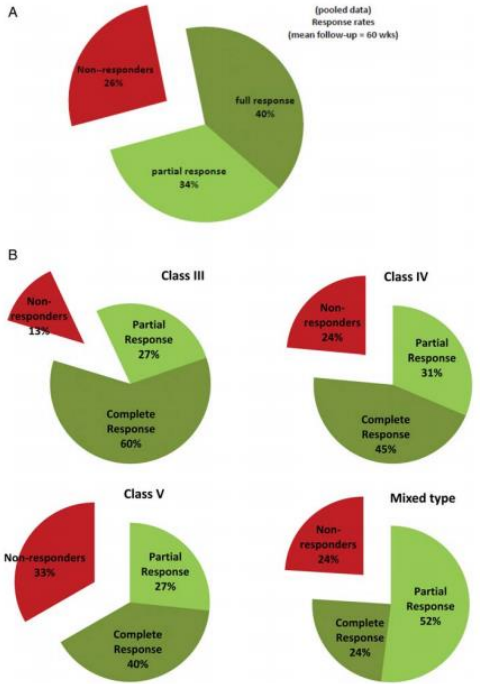
Table 2. Primary and Major Secondary Efficacy End Points in the Modified Intention-to-Treat Population.

End Point	Belimumab (N=223)	Placebo (N=223)	Difference	Odds Ratio or Hazard Ratio (95% CI)*	P Value
	Number (percent)		*percentage points*		
Primary end point: primary efficacy renal response at wk 104†	96 (43)	72 (32)	11	1.6 (1.0 to 2.3)	0.03
Major secondary end points					
Complete renal response at wk 104‡	67 (30)	44 (20)	10	1.7 (1.1 to 2.7)	0.02
Primary efficacy renal response at wk 52∫∫	104 (47)	79 (35)	11	1.6 (1.1 to 2.4)	0.02
Time to renal-related event or death¶	NA	NA	NA	0.5 (0.3 to 0.8)	0.001
Ordinal renal response without urinary sediment at wk 104|					
Complete renal reponse	67 (30)	44 (20)	10	NA	0.01
Partial renal reponse**	39 (18)	38 (17)	<1	NA	
No response	117 (52)	141 (63)	-11	NA	

All serious adverse events†	58 (26)	67 (30)
All treatment-related serious adverse events†	23 (10)	25 (11)
Most commone treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group		
Infections and infestations	15 (7)	18 (8)
Respiratory, thoracic, and mediastinal disorders	5 (2)	1 (<1)
Blood and lymphatic system disorders	3 (1)	2 (1)
Nervous system disorders	0	3 (1)
Most common treatment-related serious adverse events occurring in ≥1% of patients in either group		
Pneumonia	3 (1)	4 (2)
Herpes zoster	3 (1)	2 (1)
Adverse events resulting in discontinuation of trial drg	29 (13)	29 (13)
Adverse events of special interest‡		
Cancer		
Excluding nonmelanoma skin cancer∫∫	2 (1)	0
Including nonmelanoma skin cancer∫∫	3 (1)	0
Postinfusion reactions¶	26 (12)	29 (13)
All infections of special interest including opportunistic infections, herpes zoster, tuberculosis, and sepsis	30 (13)	34 (15)
Serious infections	9 (4)	7 (3)
Depression, suicide, or self-injury	11 (5)	16 (7)
C-SSRS suicidal ideation or behavior during trial intervention	7 (3)	12 (5)
Death	6 (3)	5 (2)
Fatal serious adverse events that began during trial intervention	4 (2)	3 (1)
Fatal serious adverse events that did not begin during trial intervention	2 (1)	2 (1)

Furie, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *New England Journal of Medicine.* 2020. 383(12), 1117-1128.

LUNAR – Revisited



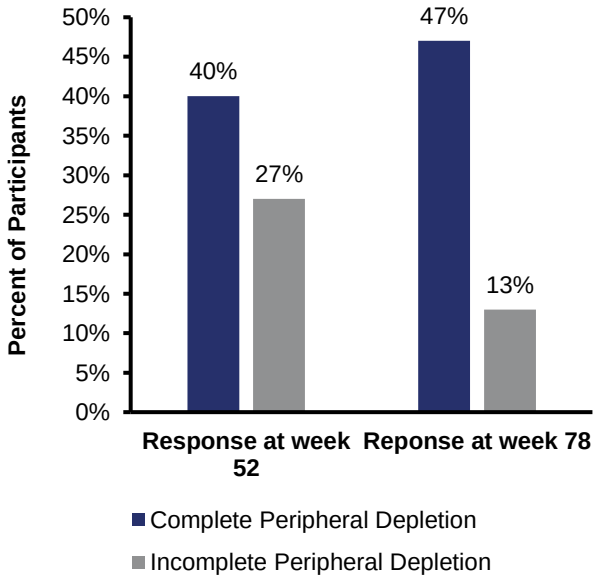


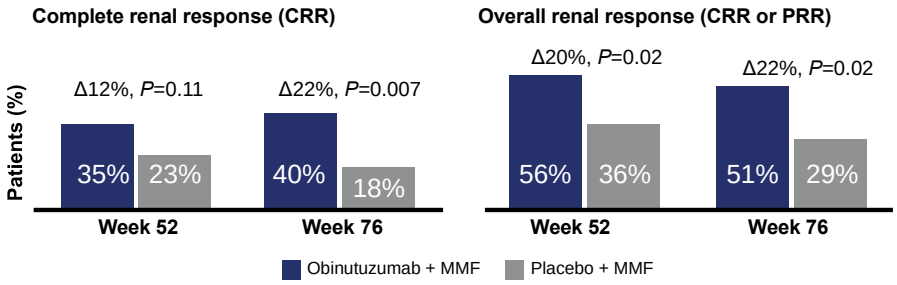
Figure 1. A larger percentage of participants from the LUNAR trial who achieved complete peripheral depletion (*n*=53) achieved complete response at week 52 and at week 78, compared to participants who did not achieve peripheral depletion (*n*=15).

Gomez Mendez, et al. *CJASN.* 2018. 13; Weidenbusch, et al. *NDT.* 2013. 28.

NOBILITY

- Obinutuzumab was associated with increased rates of CRR and ORR at Weeks 53 76 vs placebo (Figure 3).

Figure 3. Renal Response Endpoints



CONCLUSIONS

- Treatment with Obinutuzumab, a type II anti-CD20 monoclonal antibody, was associated with rapid and complete depletion of peripheral B cells and B-cell subsets and large increases in serum BAFF
- Achievement of sustained B-cell depletion was associated with increased renal response rates
- Investigation is ongoing to identify factors associated with achievement of sustained B-cell depletion and enhanced renal responses

MMF, mycophenolate mofetil; PRR, partial renal response.

Rovin, et al. B-cell depletion and response in a randomized, controlled trial of obinutuzumab for proliferative lupus nephritis. *Kidney Int Rep.* 2020. 5(3), S352.

AURORA

- Voclosporin (VCS) is a next-generation CNI
- VCS is structurally similar to cyclosporine A (CsA) but has increase potency and faster elimination- resulting in more pharmacokinetic and pharmacodynamic predictability than does CsA, **and therefore drug level monitoring is not required.**

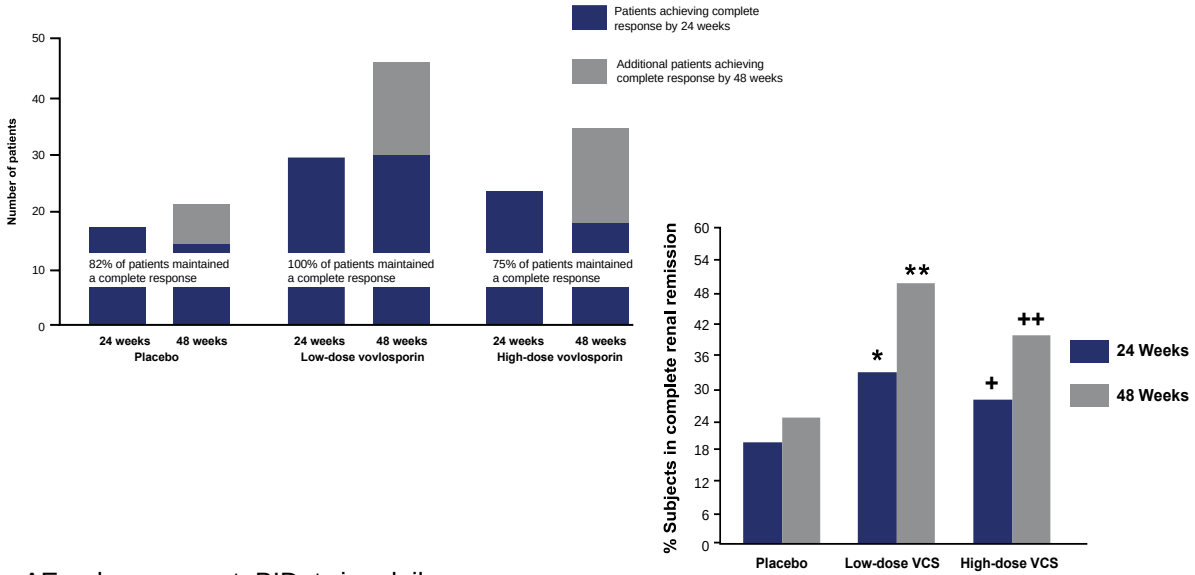


Table 2. Overall summary of adverse events (safety set, *N* = 265)

Distribution across categories of AE	Placebo (*N*=88) *n* (%)	Voclosporin 23.7mg BID (*N*=89) *n* (%)	Voclosporin 39.5mg BID (*N*=88) *n* (%)
Any AE	75 (85.2)	82 (92.1)	85 (96.6)
Any serious AE	14 (15.9)	25 (28.1)	22 (25.0)
Any treatment-related AE	15 (17.0)	45 (50.6)	55 (62.5)
Any serious treatment-related AE	1 (1.1)	4 (4.5)	7 (8.0)
Any AE leading to study drug discontinuation	9 (10.2)	16 (18.0)	14 (15.9)
Any AE with outcome of death	1 (1.1)	10 (11.2)	2 (2.3)

AE, adverse event; BID, twice daily.

Rovin, et al. *Kidney international.* 2019. 95(1), 219-231.

Take Home Messages

- Hydroxychloroquine is mainstay of SLE
- Biopsy is always necessary
- Push for combination therapy
- Push for lower dose steroids
- Needs multidisciplinary approach
- Never forget compliance
- Patients care for quality of life

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Thank you.