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Comparison of Remission and Lupus Low Disease Activity State in Damage Prevention in a United States Systemic Lupus Erythematosus Cohort

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Abstract

Objective—One objective in the treatment of SLE disease activity is to reduce long-term rates of organ damage. We analyzed data from a large clinical SLE cohort to compare patients achieving different levels of disease activity with respect to rates of long-term damage.

Methods—We analyzed data from 1,356 SLE patients in the Hopkins Lupus Cohort, followed quarterly, with 77,105 person-months observed from 1987 to 2016. Three outcome measures were considered: Clinical Remission with No Treatment, Clinical Remission On Treatment, and Lupus Low Disease Activity State (LLDAS).

Results—Patients achieved LLDAS in 50% of their follow-up while they achieved Clinical Remission with No Treatment, or Clinical Remission On Treatment in only 13% and 27% of their follow-up visits, respectively. The rates of damage consistently declined as the percentage of prior time in either LLDAS or Clinical Remission On Treatment increased. Spending a short proportion of prior time in Clinical Remission On Treatment (<25% of time) was associated with a relatively low rate of damage (1.01 per 10 person-years vs. 1.82 events per 10 person years for those never in achieving that condition, RR=0.54, p<0.0001). Those patients who experienced LLDAS at least 50% of the time had relatively low rates of damage (RR between 0.39 to 0.47, p<0.0001).

Conclusion—LLDAS is an easier target to achieve than Clinical Remission On Treatment and results in reduced risk of long-term damage. However, even a small percentage of time in Clinical Remission On Treatment was associated with reduced damage.

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Introduction

SLE disease activity is related to long-term organ damage (1)(2). One complication in the choice of a “treat to target” outcome is the fact that some treatments for disease activity (e.g. corticosteroids) might themselves increase the rates of damage. Any dose of 6–12 mg/day increases major damage by 50% (3); doses of 10 mg increase cardiovascular events 2.4-fold, with a 20 mg daily dose increasing the risk 5.1-fold (4). There is uncertainty regarding the optimal combination of disease activity target and treatment target from the perspective of long-term damage risk.

One potential treatment target is “remission”. A recent international collaborative effort, DORIS, has developed a framework for defining remission (5). This included subtypes of remission with or without abnormal serologies, and with or without low levels of treatment.

An alternative approach has been taken by Franklyn et al (6) who developed and validated criteria defining the Lupus Low Disease Activity State, or LLDAS. LLDAS is a less ambitious target than remission and allows for low levels of disease activity and treatment. LLDAS has been successfully applied post-hoc to randomized clinical trials, including anifrolumab (anti-interferon receptor monoclonal) (7), proving that it is achievable in clinical research.

Clinical trials rarely can maintain randomization beyond 12 months, which is insufficient time to ascertain differences in organ damage. Thus, longitudinal cohorts have offered the best opportunity to determine if achievement of DORIS remission or LLDAS can reduce later organ damage, and by how much.

The Hopkins Lupus Cohort allowed us to study the association between time in various types of remission and/or LLDAS and long-term organ damage. We examined not just total organ damage, but individual organ damage, as well.

Patients and Methods

Patients and data

The Hopkins Lupus Cohort is a prospective longitudinal single-center cohort of SLE patients ongoing since 1987. Patients met either SLICC or revised ACR SLE classification criteria. Patients were seen by one rheumatologist at least every 3 months, with ascertainment of the physician estimate of activity (PGA) (8) and SELENA SLE Disease Activity Index (9) and treatment. New organ damage was determined at each visit by the SLICC/ACR Damage Index (10). All patients provided informed consent and the study was approved yearly by the Johns Hopkins University School of Medicine Institutional Review Board.

This analysis is based on cohort experience prior to October 2016. Only patients who provided at least one year of cohort participation were included. This included 1,356 SLE patients of whom 55% were Caucasian, 38% African-American, and 92% were female. Their mean (SD) age at cohort entry was 38.2 (13.0) years. At cohort entry, 39% had SLE for less than a year, 28% had SLE for 1–5 years, and 33% had SLE for more than 5 years. The median SLEDAI at cohort entry was 2.0.

Definitions of Remission and LLDAS

Based on the DORIS framework, for each visit, “Clinical Remission with No Treatment” was defined as a Physician Global Assessment (PGA) <0.5, a SLEDAI=0, with no prednisone or immunosuppressant use. “Clinical Remission On Treatment” was the same but allowed prednisone ≤ 5 mg/day and maintenance treatment with immunosuppressants. “LLDAS” was defined as a SLEDAI ≤ 4 with no SLEDAI scores for the renal, CNS, serositis, vasculitis, and constitutional components, no increase in any SLEDAI component since the previous visit, PGA ≤ 1, and prednisone dose ≤ 7.5 mg/day. Immunosuppressants were allowed for LLDAS. Hydroxychloroquine treatment was allowed for all three definitions..

Statistical Methods

Using information collected at clinic visits, each visit for each patient was categorized as in remission or LLDAS based on the above definitions. Then, each month of follow-up for each patient was defined as in remission or LLDAS based on the status at the most recent past clinic visit. For each follow-up month, we determined whether a new damage event occurred in that month. The months were then classified into subgroups defined by the percentage of prior months in remission or LLDAS, and the rate of damage events in each subgroup was calculated. For ease of interpretation, rates are reported per 10 person-years. Rate ratios and associated p-values were estimated using logistic regression models fit by generalized estimating equations to account for the fact that each patient contributed multiple person-months.

The patients included in this analysis were followed for a total of 77,105 person-months. All these months were used in computing the proportion of prior months in various disease states. In estimating rates of damage by prior history of disease states, we only used months of follow-up after the first year of cohort participation. In addition, we excluded any follow-up that occurred after a gap of more than 182 days between clinic visits. These exclusions resulted in an analysis of damage over 62,189 person-months experience between 1988 and 2016. The mean number of person-months at risk per person was 46 and ranged from 1 to 292.

Results

Table 1 shows the proportion of person-months of follow-up in various states of disease activity. In 27% of the follow-up months, patients satisfied the definition of Clinical Remission On Treatment. In contrast, in 50% of the follow-up months, patients satisfied the definition of LLDAS. Over 62,189 person months of follow-up, we observed 595 new damage events. This corresponds to 1.15 events per 10 person-years.

Table 2 shows the rates of damage in sub-groups defined by percentage of prior cohort follow-up in remission or LLDAS. For each type of remission/LLDAS, the rates of damage decreased as the percentage of prior time in remission/LLDAS increased. Those who had been in Clinical Remission On Treatment at any point in time but even less than 25% of their follow-up had substantially lower rates of damage than those who were never in that

condition (RR=0.54, $p<0.0001$). Patients with a small proportion of time in LLDAS did not experience a comparable reduction in damage rates. On the other hand, those patients who experienced LLDAS at least 50% of the time had relatively low rates of damage (between 0.75 and 0.88 events per 10 person-years). This LLDAS target was relatively easy to achieve (satisfied in approximately 50% of the person-months of follow-up).

Because experience of prior damage is a strong predictor of future damage, we performed the analyses shown in Table 2 separately for those with no prior damage, those with a SLICC damage index of 1, and those with a SLICC damage index of 2 or more. The results can be seen in supplementary material. For those months of follow-up among those with no prior damage the pattern is similar to what is seen in Table 2 (Supplementary Table 1). For those months after which a person has had one previous damage event, there was generally less of an association between damage and time spent in LLDAS and Clinical Remission on Treatment (Supplementary Table 2). Finally, for those months after which a person has 2 or more previous items of damage, there were strong associations between subsequent damage and prior LLDAS and remission, and even a small proportion of previous time in LLDAS was associated with a large reduction in damage risk (Supplementary Table 3).

Tables 3 and 4 shows the effect of achieving LLDAS or Clinical Remission On Treatment on individual organ damage items as defined by the SLICC/CR Damage Index. Both LLDAS and Clinical Remission On Treatment were associated with significantly reduced rates of musculoskeletal, renal, osteoporosis damage, and premature gonadal failure. LLDAS was also associated with a lower risk of diabetes, myocardial infarction and seizures. There was no evidence of a relationship between either remission or LLDAS and risk of cataract, malignancy, pulmonary, or eye organ damage.

We found a substantially higher level of activity among African Americans than Caucasians. Caucasians had 58% of follow-up (out of 41,860 months) in LLDAS and 32% in Clinical Remission On Treatment. African-Americans had only 41% of follow-up (out of 30,255 months) in LLDAS and 19% in Clinical Remission On Treatment ($p<0.0001$ for each difference). This increased level of disease activity was not explained by socioeconomic status as represented by education ($P<0.0001$ for each comparison after adjusting for years of education). Table 5 shows the relationship between damage and LLDAS or Clinical Remission On Treatment separately by ethnicity. In both Caucasians and African Americans, a reduced rate of damage was strongly associated with LLDAS or Clinical Remission.

Discussion

This is the largest study (based on number of patients and length of follow up) of DORIS remission and LLDAS as predictors of organ damage. Because patients were followed by protocol quarterly, and all indices were completed by one rheumatologist, we were able to reduce variation and to avoid biases of different follow up intervals based on disease activity. Our analysis used percentage of months (rather than “consecutive years”), to reflect that over years of follow up most patients have flares, temporarily leaving remission or LLDAS. Also, unlike previous analyses, we examined the association between prior experience of

remission or LLDAS and subsequent damage, rather than the association between remission or LLDAS and damage that occurred in the same interval of time.

First, we showed that even a small percentage of time (<25%) in DORIS Clinical Remission with minimal treatment led to an approximately 50% reduction in organ damage. A longer period of time in LLDAS was required to achieve a comparable reduction in organ damage.

Secondly, we showed that patients who satisfied the criteria for LLDAS over 50% of their follow-up achieved a substantial reduction in damage. This is noteworthy since this may be an easier target to achieve. Fully 50% of the follow-up time of our cohort satisfied this condition. The fact that those who achieve LLDAS >50% of the time have just as low risk as those who achieve the more stringent targets of clinical remission >50% may be due to sampling variability. But if this association is real, it has implications regarding the treatment target for those with relatively good disease control.

Third, we showed that being in LLDAS > 50% of the time did not prevent all types of organ damage. In particular, it prevented musculoskeletal, central nervous system, renal, osteoporotic fractures and myocardial infarction. There was no evidence that time in LLDAS prevented cataract (likely as even low dose prednisone use contributes to cataract). It did not prevent pulmonary fibrosis or pulmonary hypertension. It did not prevent cognitive impairment. Thus, much as we believe that reduction in both disease activity and prednisone is our optimum clinical outcome, we are obviously missing some additional factors that lead to important organ damage.

Fourth, we found that African-Americans have substantially more disease activity than Caucasians even after adjusting for years of education, leading to a decreased chance of achieving either LLDAS or Clinical Remission. However, the same relationship holds true that achieving LLDAS or Clinical Remission leads to a significant reduction in organ damage. This is consistent with a previous analysis of our cohort where we showed that rates of damage were significantly higher among African American patients, but after adjustment for disease activity and other variables, this disparity was substantially reduced (1).

Our findings are consistent with recent studies of new definitions of LLDAS and remission. In their seminal paper on LLDAS, Franklyn found that patients in their cohort with more than 50% of their follow-up in LLDAS had an average increase in damage score of 0.57 points less than those with more disease activity during an average of 3.9 years of follow-up per person. Their cohort had somewhat more disease activity than ours, with an average of only 39% of follow-up in the LLDAS, compared to 50% in ours. In 293 Italian Caucasian patients, patients with two consecutive years in LLDAS had less damage accrual (11). In 183 patients with a median 5-year follow up, both LLDAS or remission > 50% of observable visits reduced organ damage (12). However, we are the first study to show a comparison of DORIS remission and LLDAS, the first study to include a large number of African-Americans, and the first study to include damage to individual organs (and not just total damage).

Our findings on the rate of achievement of LLDAS and remission, and the number of subsequent damage events might be useful to those planning clinical trials of the impact of

reducing disease activity on damage. In clinical trials, LLDAS seems to be a very reasonable outcome measure, with trials already showing that it is achievable. In clinical practice, remission would remain the best (but hard to achieve) goal.

A limitation of our study is that it is based on disease activity measures and damage accrual over a 30 year period. The relationship between disease activity, treatment, and damage accrual may be somewhat different today given new approaches to patient management

Another limitation of analyses of observational studies such as ours or those cited above is that they cannot establish a causal relationship between disease activity and damage. Thus, for example, increased SLE disease activity might reflect an unknown underlying condition that also leads to increased risk of damage. If that is the case, then reducing disease activity would not result in the decline in damage risk to the same degree observed in these studies.

Just as all types of SLE damage are not associated with SLE disease activity, all manifestations of SLE disease activity are not associated with damage. Therefore, an alternative to setting the target of overall low disease activity would be to specifically target specific types of disease activity that are associated with specific types of damage. These relationships need to be identified. For example, in previous work, we have tried to identify specific risk factors for cardiovascular events (4), cataract (13), seizures (14), and depression (15).

In conclusion, DORIS Remission On Treatment even for a small percentage of visits, reduces later organ damage. LLDAS 50% of the time reduces organ damage by about 50%. However, not all types of individual organ damage items are reduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Number (percent) of follow-up months in which the patient was in various states of SLE disease activity.

State of Disease Activity	Number (percent) of follow-up months state (n=77,105)
LLDAS	38,880 (50%)
Clinical Remission On Treatment ¹	20,489 (27%)
Clinical Remission with No Treatment ²	10,347 (13%)

¹Requires Prednisone dose $\leq$ 5 mg/day, but allows for maintenance immunosuppressants and hydroxychloroquine.

²Requires no use of prednisone or immunosuppressants, but allows for use of hydroxychloroquine

Table 2

Rates of new damage, in subgroups defined by past levels of disease activity

Percentage of Prior Months in:	Number of person-years observed	Number of damage events.	Rate of events per 10 person years	Rate Ratios (95% Confidence Intervals)	P-values
LLDAS					
None	638	117	1.83	1.0 (Ref)	
Not none, but < 25%	880	134	1.52	0.80 (0.61, 1.06)	0.12
25% to 50%	1057	129	1.22	0.63 (0.48, 0.84)	0.0012
50% to 75%	1513	133	0.88	0.47 (0.36, 0.62)	<0.0001
75%+	1095	82	0.75	0.39 (0.29, 0.53)	<0.0001
Clinical Remission On Treatment ¹					
None	1374	250	1.82	1.0 (Ref)	
Not none, but < 25%	1681	170	1.01	0.54 (0.44, 0.67)	<0.0001
25% to 50%	1195	103	0.86	0.47 (0.36, 0.60)	<0.0001
50% to 75%	700	54	0.77	0.43 (0.30, 0.60)	<0.0001
75%+	232	18	0.77	0.45 (0.27, 0.75)	0.0019
Clinical Remission No Treatment ²					
None	2981	406	1.36	1.0 (Ref)	
Not none, but < 25%	1197	102	0.85	0.60 (0.48, 0.75)	<0.0001
25% to 50%	548	50	0.91	0.66 (0.46, 0.94)	0.023
50% to 75%	320	27	0.84	0.63 (0.42, 0.97)	0.035
75%+	137	10	0.73	0.58 (0.30, 1.15)	0.12

¹ Requires Prednisone dose ≥ 5 mg/day, but allows for maintenance immunosuppressants and hydroxychloroquine.² Requires no use of prednisone or immunosuppressants, but allows for use of hydroxychloroquine

Table 3

Numbers of specific types of damage events (rate per 10 person-years) in groups classified by prior LLDAS experience.

Damage Type	Percentage of Prior visits in LLDAS					P-value for trend ²
	None (638 PY) ¹	<25% (880 PY) ¹	25–50% (1057 PY) ¹	50–75% (1513 PY) ¹	75%+ (1095 PY) ¹	
Arthritis (deforming or erosive)	9 (0.15)	6 (0.08)	1 (0.01)	6 (0.04)	1 (0.01)	0.0010
Avascular Necrosis	12 (0.23)	14 (0.20)	4 (0.05)	7 (0.05)	1 (0.01)	<0.0001
Cataract	12 (0.23)	16 (0.23)	11 (0.13)	27 (0.21)	16 (0.17)	0.38
Cognitive Impairment	1 (0.02)	4 (0.05)	7 (0.07)	3 (0.02)	7 (0.07)	0.71
Cardiomyopathy	4 (0.07)	4 (0.05)	3 (0.03)	4 (0.03)	1 (0.01)	0.053
Cranial or Peripheral Neuropathy	3 (0.05)	7 (0.09)	9 (0.10)	8 (0.06)	3 (0.03)	0.26
Cerebrovascular Accident	5 (0.09)	5 (0.06)	4 (0.04)	4 (0.03)	6 (0.06)	0.34
Diabetes mellitus	3 (0.05)	6 (0.07)	3 (0.03)	3 (0.02)	1 (0.01)	0.020
End Stage Renal Disease	11 (0.18)	3 (0.04)	3 (0.03)	1 (0.01)	1 (0.01)	0.0001
Glomerular Filtration Rate <50%	7 (0.12)	1 (0.01)	0 (0.00)	1 (0.01)	0 (0.00)	0.0046
Infarction or resection of bowel below duodenum	4 (0.07)	8 (0.11)	10 (0.11)	3 (0.02)	6 (0.06)	0.076
Malignancy	6 (0.10)	9 (0.11)	11 (0.11)	11 (0.08)	8 (0.08)	0.66
Myocardial Infarction	7 (0.11)	3 (0.04)	7 (0.07)	3 (0.02)	2 (0.02)	0.0077
Osteomyelitis	4 (0.06)	1 (0.01)	1 (0.01)	0 (0.00)	1 (0.01)	0.037
Osteoporosis with fracture or vertebral collapse	18 (0.31)	18 (0.24)	20 (0.22)	22 (0.16)	14 (0.14)	0.0051
Pleural Fibrosis	4 (0.06)	4 (0.05)	5 (0.05)	5 (0.03)	1 (0.01)	0.11
Premature gonadal failure	4 (0.07)	4 (0.05)	1 (0.01)	0 (0.00)	0 (0.00)	0.0046
Pulmonary Fibrosis	9 (0.16)	3 (0.04)	9 (0.10)	9 (0.06)	11 (0.11)	0.93
Pulmonary Hypertension	2 (0.03)	5 (0.06)	11 (0.11)	9 (0.06)	6 (0.06)	0.99
Retinal change or optic atrophy	1 (0.02)	4 (0.05)	4 (0.04)	5 (0.03)	2 (0.02)	0.93
Ruptured Tendon	1 (0.02)	3 (0.03)	5 (0.05)	3 (0.02)	4 (0.04)	0.63
Seizures requiring therapy for at least 6 months	4 (0.07)	1 (0.01)	4 (0.04)	1 (0.01)	1 (0.01)	0.038
Valvular Disease	2 (0.03)	2 (0.02)	8 (0.08)	5 (0.03)	0 (0.00)	0.19

¹ PY=Person-years. The actual number of PY used to calculate rates for each damage item varies somewhat because follow-up after damage of that type occurs is not included.

²Based on a logistic regression model treating LLDAS percentage as a quantitative predictor.

Table 4

Numbers of specific types of damage events (rate per 10 person-years) in groups classified by prior Clinical Remission on Treatment experience.

Damage Type	Percentage of Prior visits in Clinical Remission On Treatment				P-value for trend ²
	None (1374 PY ¹)	<25% (1681 PY ¹)	25–50% (1195 PY ¹)	50–75% (700 PY ¹)	75%+ (232 PY ¹)
Arthritis (deforming or erosive)	10 (0.08)	8 (0.05)	3 (0.03)	2 (0.04)	0 (0.00)
Avascular Necrosis	25 (0.22)	9 (0.06)	3 (0.03)	0 (0.00)	1 (0.05)
Cataract	27 (0.25)	24 (0.18)	20 (0.20)	7 (0.11)	4 (0.18)
Cognitive Impairment	5 (0.04)	7 (0.05)	5 (0.05)	5 (0.08)	0 (0.00)
Cardiomyopathy	7 (0.05)	3 (0.02)	1 (0.01)	4 (0.06)	1 (0.04)
Cranial or Peripheral Neuropathy	11 (0.09)	11 (0.07)	5 (0.05)	3 (0.05)	0 (0.00)
Cerebrovascular Accident	11 (0.09)	5 (0.03)	2 (0.02)	4 (0.06)	2 (0.09)
Diabetes mellitus	7 (0.06)	6 (0.04)	2 (0.02)	1 (0.01)	0 (0.00)
End Stage Renal Disease	14 (0.11)	2 (0.01)	2 (0.02)	1 (0.01)	0 (0.00)
Glomerular Filtration Rate <50%	8 (0.06)	0 (0.00)	0 (0.00)	1 (0.01)	0 (0.00)
Infarction or resection of bowel below duodenum	12 (0.10)	11 (0.08)	4 (0.04)	2 (0.03)	2 (0.09)
Malignancy	16 (0.13)	10 (0.07)	13 (0.12)	6 (0.09)	0 (0.00)
Myocardial Infarction	9 (0.07)	7 (0.04)	3 (0.03)	3 (0.03)	0 (0.00)
Osteomyelitis	6 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Osteoporosis with fracture or vertebral collapse	34 (0.28)	31 (0.22)	13 (0.12)	11 (0.17)	3 (0.13)
Pleural Fibrosis	9 (0.04)	6 (0.04)	3 (0.03)	1 (0.01)	0 (0.00)
Premature gonadal failure	6 (0.05)	3 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)
Pulmonary Fibrosis	13 (0.10)	7 (0.05)	14 (0.13)	6 (0.09)	1 (0.05)
Pulmonary Hypertension	10 (0.08)	12 (0.08)	8 (0.07)	1 (0.01)	2 (0.09)
Retinal change or optic atrophy	5 (0.04)	4 (0.03)	6 (0.05)	0 (0.00)	1 (0.05)
Ruptured Tendon	4 (0.03)	7 (0.04)	4 (0.03)	1 (0.02)	0 (0.00)
Seizures requiring therapy for at least 6 months	7 (0.05)	1 (0.01)	3 (0.03)	0 (0.00)	0 (0.00)
Valvular Disease	6 (0.05)	4 (0.02)	4 (0.03)	3 (0.04)	0 (0.00)

¹ PY=Person-years. The actual number of PY used to calculate rates for each damage item varies somewhat because follow-up after damage of that type occurs is not included.

² Based on a logistic regression model treating LLDAS percentage as a quantitative predictor.

Table 5
Rates of new damage in subgroups defined by past levels of disease activity by ethnicity

Percentage of Prior Months in:	Number of person-years observed	Number of damage events	Rate of events per 10 person years	Rate Ratios (95% Confidence Intervals)	P-values
LLDAS - Caucasians					
None	225	45	2.00	1.00 (Ref)	
Not none, but < 25%	344	58	1.68	0.79 (0.49, 1.26)	0.32
25% to 50%	495	74	1.49	0.68 (0.45, 1.04)	0.075
50% to 75%	904	83	0.92	0.44 (0.29, 0.67)	0.0002
75%+	836	65	0.78	0.36 (0.23, 0.55)	<0.0001
Clinical Remission on Treatment ¹ -Caucasians					
None	576	116	2.01	1.00 (Ref)	
Not none, but < 25%	832	90	1.08	0.51 (0.38, 0.70)	<0.0001
25% to 50%	734	65	0.88	0.44 (0.30, 0.62)	<0.0001
50% to 75%	485	40	0.82	0.40 (0.27, 0.61)	<0.0001
75%+	178	14	0.79	0.43 (0.24, 0.78)	0.0059
LLDAS – African-Americans					
None	356	65	1.82	1.0 (Ref)	
Not none, but < 25%	480	67	1.39	0.76 (0.54, 1.07)	0.13
25% to 50%	468	49	1.05	0.57 (0.39, 0.83)	0.0029
50% to 75%	528	45	0.85	0.46 (0.31, 0.68)	<0.0001
75%+	219	14	0.64	0.35 (0.19, 0.61)	0.0003
Clinical Remission on Treatment ¹ -African-Americans					
None	699	121	1.73	1.0 (Ref)	
Not none, but < 25%	755	73	0.97	0.56 (0.41, 0.75)	0.0002
25% to 50%	375	31	0.83	0.47 (0.32, 0.70)	0.0002
50% to 75%	186	14	0.75	0.43 (0.20, 0.90)	0.026
75%+	36	1	0.28	0.16 (0.02, 1.18)	0.072

¹ Requires Prednisone dose ≥ 5 mg/day, but allows for maintenance immunosuppressants and hydroxychloroquine.