Longitudinal Disease Activity, Damage Accrual, and Treatment Exposure in Systemic Lupus Erythematosus With Lupus Nephritis: Insights From the Lupus Federated Data Network (LupusNet)

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Key Takeaways

- **These data highlight a disconnect between disease activity control, exposure to multiple treatments, and long-term damage in patients with SLE, according to their LN status**
- **Patients with LN required greater treatment intensity and accumulated organ damage at a higher rate compared with those without LN, with a +0.6-point increase in SDI score from registration to Year 3 (vs +0.4 points for those without LN; *P*=0.03)**
- **Patients with LN who were enrolled in LupusNet experienced a reduction in their disease activity in the year after registration (–4.4 points in SLEDAI-2K score)**
- **Patients without LN continued to accrue damage (+0.4 points in SDI score) despite steady disease activity (–0.3 points in SLEDAI-2K score); a substantial proportion did not have exposure to additional treatments**
- **These findings highlight the need for outcome frameworks and treatment strategies (eg, earlier and more efficacious treatments) to prevent irreversible long-term organ damage across patients with and without LN**

Background

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by a heterogeneous clinical presentation[1]
- Lupus nephritis (LN) is a major organ manifestation of SLE that affects approximately 40% of patients with SLE and is associated with substantial morbidity and mortality[2]
  - The presence of LN often leads to earlier and more intensive immunosuppressive treatment[3]
- However, real-world evidence remains limited on how LN influences longitudinal control of disease activity, damage accrual, and treatment escalation in patients with SLE
- The Lupus Federated Data Network (LupusNet) harmonizes data from existing longitudinal SLE registries across multiple geographic regions, which enables consistent analyses of clinical characteristics and outcomes while data remain within the participating networks[4]
  - LupusNet currently aggregates data from 5 major, longitudinal, observational registries of patients with SLE that are located in the Asia-Pacific region, North America, Europe, and Latin America
  - The registries include the Asia Pacific Lupus Collaboration (APLC), The National Databank for Rheumatic Diseases (FORWARD), the Lupus Register of the Spanish Society of Rheumatology (RELESSER), the Grupo Latino Americano De Estudio de Lupus (GLADEL 2.0), and the Almenara Lupus Cohort (Almenara)

Objective

Using harmonized data from participating SLE registries in LupusNet, this analysis compared longitudinal disease activity severity, damage accrual, and treatment exposure in a large cohort of SLE patients with LN versus those without LN

Methods

- Data from 4 SLE registries mapped within LupusNet were included: APLC (Asia Pacific), RELESSER (Europe), and Almenara and GLADEL 2.0 (Central and South America)
  - Disease activity and damage were evaluated using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) scores
- Patients with ≥3 years of follow-up from enrollment in the registry (registration) were included
  - Patients were classified according to the presence or absence of LN at registration
    - LN was identified using an operational definition (ie, the SLEDAI-2K proteinuria item at registration) rather than clinically adjudicated LN
- Longitudinal changes in disease activity severity, organ damage, and treatment exposure were compared between patients with and without LN
  - Disease activity severity was assessed using the maximum observed SLEDAI-2K score between registration and Year 3, categorized as mild (≤4), moderate (>4 to <10), or high (≥10)
  - Organ damage severity was assessed using the maximum observed SDI score
- Treatment exposure was assessed using the number of distinct immunosuppressants (eg, conventional immunosuppressants, conventional disease-modifying antirheumatic drugs [DMARDs], targeted synthetic DMARDs) or biologics received between registration and Year 3

Results

Demographic Characteristics

- A total of 3734 patients were included in the analysis, including 626 (16.8%) with LN and 3108 (83.2%) without LN (**Table 1**)
  - Patients with LN tended to be younger (mean age, 36.8 vs 43.5 years; absolute standardized difference [ASD], 0.524) and have a shorter time from diagnosis to registration (mean time, 8.8 vs 11.1 years; ASD, 0.286) compared with patients without LN
  - At registration, patients with LN were more likely to have moderate-to-high disease activity compared with patients without LN (moderate, 26.2% vs 29.1%; high, 68.4% vs 18.4%, respectively); for patients with mild, moderate, and high disease activity, LN was present in 2.0% (34 of 1666), 15.4% (164 of 1068), and 42.8% (428 of 1000) of patients, respectively

TABLE 1: Patient characteristics at registration

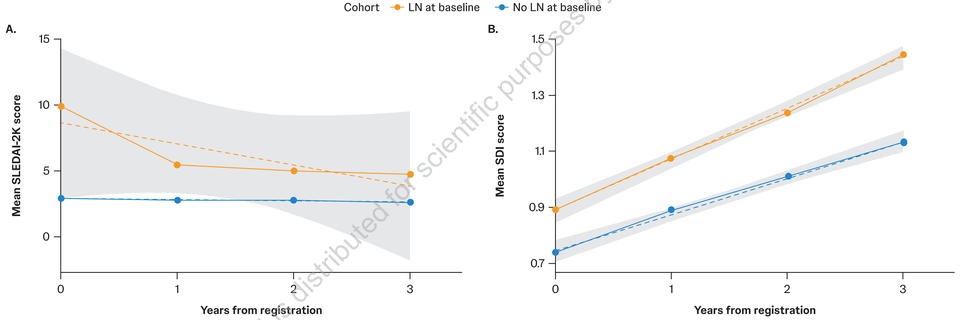
	With LN	Without LN
n at registration (% of overall)	626 (16.8)	3108 (83.2)
Mean (SD) age, y	36.8 (11.8)	43.5 (13.0)
Female sex, n (%)	547 (87.4)	2883 (92.8)
Mean (SD) time from diagnosis to registration, y	8.8 (7.8)	11.1 (8.1)
SLE disease activity,* n (%)		
Mild	34 (5.4)	1632 (52.5)
Moderate	164 (26.2)	904 (29.1)
High	428 (68.4)	572 (18.4)
Mean (95% CI) SLEDAI-2K score	9.9 (7.5-12.3)	2.9 (2.3-3.5)
Mean (95% CI) SDI score	0.9 (0.3-1.5)	0.7 (0.5-0.9)

*Mild: SLEDAI-2K score ≤4; moderate: SLEDAI-2K score >4 to <10; high: SLEDAI-2K score ≥10. Because the SLEDAI-2K proteinuria item contributes +4 points to the SLEDAI-2K score, all patients in the LN cohort had a SLEDAI-2K score ≥4.
CI=confidence interval, **LN**=lupus nephritis, **SD**=standard deviation, **SDI**=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, **SLE**=Systemic Lupus Erythematosus, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.

Course of Disease for Patients With LN Through the 3-Year Follow-Up

- Patients with LN at registration experienced greater reductions in mean SLEDAI-2K scores during the 3-year follow-up (–5.2 points) compared with patients without LN (–0.3 points; **Figure 1A**)
  - In patients with LN, a sharp reduction in mean disease activity was observed during the first year after registration (–4.4 points)
- Patients with LN accrued organ damage at a slightly higher rate, with greater increases in mean SDI scores from registration to Year 3 (+0.6 points) than in patients without LN (+0.4 points; *P*=0.03; **Figure 1B**)

FIGURE 1: (A) Mean disease activity scores and (B) mean organ damage scores, with best-fit linear lines

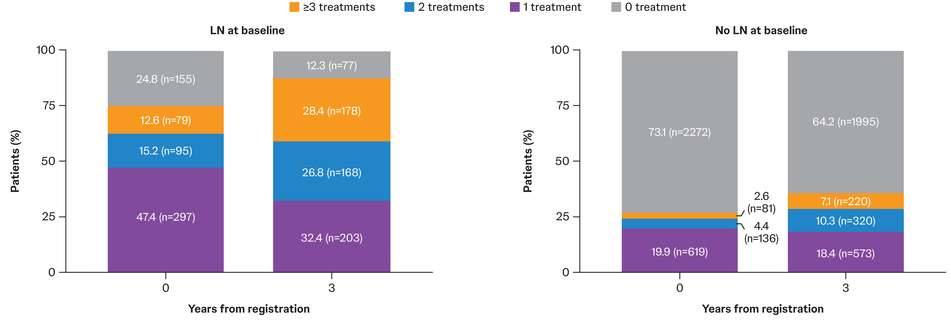


Dotted lines are ordinary least-squares best-fit linear lines; shaded bands represent 95% CIs for the best-fit lines.
CI=confidence interval, **LN**=lupus nephritis, **SDI**=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.

Treatment With Immunosuppressants and Biologics

- The majority of patients with LN and moderate-to-high disease activity required treatment with ≥1 immunosuppressant or biologic at registration (75.2%) compared with 26.9% of patients with moderate-to-high disease activity without LN; by Year 3, the proportion of patients exposed to ≥1 treatment increased in both groups (**Figure 2**)
  - A substantial proportion of patients without LN received no immunosuppressants or biologics at registration (73.1%) and by Year 3 (64.2%)
- A greater proportion of patients with LN received ≥2 immunosuppressants or biologics at registration and by Year 3 compared with patients without LN

FIGURE 2: Exposure to immunosuppressants or biologics at registration and by Year 3 in patients with moderate-to-high SLE disease activity, with and without LN



Treatments assessed include abatacept, adalimumab, azathioprine, belimumab, certolizumab, cyclophosphamide, cyclosporine, etanercept, golimumab, leflunomide, methotrexate, mycophenolate mofetil, mycophenolic acid, penicillamine, rituximab, sulfasalazine, tacrolimus, tocilizumab, and tofacitinib.
LN=lupus nephritis, **SLE**=systemic lupus erythematosus.

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