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Rev Invest Clin. 2022;74(5):227-31 BRIEF REVIEW

Update on Novel Blood-Based Biomarkers for Lupus Nephritis Beyond Diagnostic Approaches

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with a wide range of clinical presentations. Lupus nephritis (LN) is a frequent complication of SLE, representing a significant cause of morbidity and mortality in these patients. In addition, LN diagnosis remains suboptimal in most clinical contexts. The current gold standard for LN clinical diagnosis is a renal biopsy. Still, the invasiveness of this technique is an obstacle to the early detection of renal involvement and further monitoring of treatment results. Consequently, there are different areas for improvement in the field of LN, such as the search for novel non-invasive clinical biomarkers with an adequate correlation between clinical manifestations and actual histological damage. Although urine component-related studies are promising, the more robust blood/serum biomarkers may still be helpful in developing point-of-care systems that can be adapted to most clinical scenarios. Therefore, this brief review aims to highlight and summarize some of the most recently reported non-classical serum/blood potential LN biomarkers. (REV INVEST CLIN. 2022;74(5):227-31)

Keywords: Lupus nephritis. Biomarker. Diagnostics. Prognosis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous and multifactorial autoimmune disease, revealed by autoantibody production and dysregulated high expression of Type I interferon (IFN)-stimulated genes, causing a wide variety of clinical manifestations[1]. About 50-80% of SLE patients will develop lupus nephritis (LN), which represents a significant cause of morbidity and mortality in these patients[2,3]. In the last decade, therapeutic approaches for LN have remained essentially unchanged, with a probability of achieving complete or partial remission not beyond 60-70%; unfortunately, the rest of the patients usually progresses to end-stage renal disease within 5 years after the onset[4,5]. Moreover, LN diagnosis and/or monitoring remain suboptimal in most clinical contexts. Besides the low possibility of causing kidney damage and being an invasive procedure, renal biopsy represents the gold standard for LN diagnosis and to determine the degree of tissue involvement5; furthermore, its usefulness in directing the choice of one

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therapeutic approach over another is still limited[2,4,6,7]. Consequently, there are different areas for improvement in the field of LN, such as the optimization of long-standing treatment strategies and the search for novel therapeutic agents to improve outcomes such as mortality or development of end-stage renal disease. Among these issues, one of the most relevant is the search for new clinical biomarkers with a good correlation between clinical manifestations and actual histological damage that allow the follow-up of patients with LN to guide personalized treatments.

In recent years, the investigation of LN biomarkers has produced many publications; however, the same serum and urinary measurements have continued to be used in clinical practice for over three decades. These conventional diagnostic and prognostic LN biomarkers include proteinuria, hematuria, urinary casts, serum creatinine levels, anti-double-stranded DNA autoantibodies, and complement levels[5,7]. Given the heterogenetic nature of LN patients and the not-yet reached needs in precision diagnosis and classification of these individuals in terms of personalized therapy, identification of novel biomarkers would be helpful to provide auxiliary information about the disease activity, the early recognition of renal flares, treatment selection, and responsiveness to a particular medication scheme. Although urine component-related studies are promising, the more robust blood/serum biomarkers may still be useful in developing point-of-care systems that can be adapted to most clinical settings or even home testing of LN.

NOVEL BLOOD/SERUM BIOMARKERS FOR LUPUS NEPHRITIS

A relatively large number of non-classical blood/serum candidate biomarkers have been evaluated in LN cohorts. Most of these candidates have only been assessed in cross-sectional analyses, with few reports of markers prospectively evaluated. Limitations of most-recent studies also include the relatively small number of patients tested and the lack of confirmation by independent research groups. Although further validation must be performed in most cases, the following candidates, not yet incorporated into routine clinical practice, still represent promising alternatives to enhance the diagnostic accuracy, prognostic stratification, and monitoring of treatment response in LN patients. Detailed information will be next presented for these potential LN biomarkers, while these and some of the most recently reported candidates are enumerated in table 1.

MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1 OR CCL_2)

Monocyte chemoattractant protein 1 (MCP-1 or CCL2) belongs to the C-C chemokine family[8]. Increased expression of this chemokine on epithelial or endothelial cells and infiltrating mononuclear leukocytes in the tubulointerstitial regions can be demonstrated in kidney biopsies of LN patients[8,9]. In addition, different studies have found a potential diagnostic or prognostic value for this molecule in the context of LN; some reported an association between increased levels of MCP-1/CCL2 and LN, while others looked at its prognostic role through renal disease activity as an outcome, showing significant correlations with the chemokine circulating levels[7,8].

SURROGATE MARKERS OF TYPE I INTERFERON SIGNATURE

SLE patients are characterized by an increased expression of type I IFN-regulated genes[10], indicated as an IFN gene signature that comprises some LN biomarker candidates, including SIGLEC-1, CXCL10, and Galectin-9. The sialic acid-binding Ig-like lectin 1 (SIGLEC-1) is a cell-adhesion molecule involved in the initial contact of phagocytic cells with sialylated pathogens[11]. It could also be found in its soluble form in serum, where elevated concentrations have been associated with increased frequency of renal complications but not with SLE disease activity index[7,12].

CXCL10 is a chemokine that has shown a high correlation with SLE activity and the best predictive ability for flares among chemokines regulated by IFN-I[8,13]. Remarkably, renal flares are accurately predicted by CXCL10 serum levels but not by classical biomarkers such as complement levels or anti-double-stranded DNA autoantibodies[7,8]. Furthermore, the β-galactoside-binding lectin Galectin-9 has shown a higher correlation with SLE activity than CXCL10 levels. Interestingly, in the context of LN, serum levels of Galectin-9 also reflect kidney damage and not only SLE activity[7,14].

Table 1. Blood/serum novel biomarkers for LN

Response/prognosis/ diagnosis	Biomarker tested	LN patients	Activity score used
Diagnosis	HMGB-1	37	SLEDAI
	Anti-ENO1 combined with β2 microglobulin	29	SLEDAI 2K
	Expression of circRNAs	30	SLEDAI 2K, rSLEDAI
	IL-35	80	SLEDAI 2K
	HE4	44	SLEDAI
Diagnosis/prognosis	miR-203	109	UK
	NETs; Nox2	35	SLEDAI, rSLEDAI, SLICC/ACR DI
	miR family	30	SLEDAI 2K, ACR
	Anti-MDA Ab	148	SLEDAI 2K, SLAM, SLICC/ACR DI, BILAG
	IL-1β and IL-18	58	SLEDAI 2K, rSLEDAI
	microRNA-200 family	101	SLEDAI
Prognosis	MCP-1	67	SLEDAI
	Galectin-9	97	SLEDAI, SLICC, SLEDAI 2k
	IL-17A	85	SLEDAI 2K, BILAG 2004
	Anti-ribosomal P antibody	79	SLEDAI 2K, AI + CI
	a-PLA2R	98	SLEDAI 2K, rSLEDAI, SLICC/ACR DI, AI + CI
	Osteopontin	75	SLEDAI 2K, SLEDAI, SLICC/ ACR DI
	sMer, sAxl, and GAS6	68	SLEDAI, AI + CI
	CD25	34	SLEDAI
	C4d	45	SLEDAI, SLEDAI 2K
Response	Aged-associated B cells (ABCs), CD21hi B cells	26	SLEDAI, SLICC/ ACR
	Galectin-3	33	rSLEDAI, SLEDAI
	Axl	52	SLEDAI 2K, AI + CI
Response/prognosis	Glycoproteinacetylation	36	SLEDAI 2K
	Sclerostin	50	SLICC/ACR DI, SLEDAI, AI + CI
	CXCL10 and Vitamin D	25	SLEDAI, AI
	IL17, IL-23	80	SLEDAI, AI + CI

Lupus nephritis potential blood/serum biomarkers. All biomarkers were reported from 2018 to 2022[6-8,18,22]. LN: lupus nephritis; Activity Scores - SLEDAI: systemic lupus erythematosus activity index; rSLEDAI: renal SLEDAI; ACR: American College of Rheumatology; AI: activity index; CI: chronicity index; SLICC: systemic lupus international collaborating clinics; BILAG: British Isles lupus assessment group; Biomarkers - Anti-ENO1: anti-α-enolase antibody; Anti-MDA: IgG anti-malondialdehyde protein; GAS6: growth arrest specific protein 6; HE4: human epididymis protein; HMGB-1: high-mobility group box-1; MCP-1: monocyte chemoattractant protein-1; NETs: neutrophil extracellular traps assay; Nox2: NADPH oxidase.

INTERLEUKIN-18

Interleukin-18 (IL-18) is a member of the IL-1 family of cytokines constitutively present (as a precursor) in nearly all human cells[15]. The activity of IL-18 is balanced by the presence of a high affinity, naturally-occurring IL-18 binding protein (IL-18BP)[15]. These molecules have been extensively investigated in SLE and proposed as a biomarker of disease activity that correlates with other serological markers (anti-dsDNA and complement levels)[16,17]. Interestingly, active nephritis is the primary SLE manifestation associated with elevated IL-18 and IL-18BP levels[7,18].

LYMPHOCYTE POPULATIONS

Although several circulating lymphocyte subsets have been reported to act as SLE markers, including plasmablasts ($CD19^{lo}$ $CD27^{hi}$ $CD38^{hi}$)[19], transitional B cells ($CD24^{hi}$ $CD38^{hi}$)[20], and follicular helper T cells ($CD4^{+}$ $CXCR5^{+}$)[21], none of them are currently linked to nephritis complication[6].

Interestingly, our group recently confirmed the potential utility of the $CD11c^{+}$ T-bet^{+} $CD21^{lo/-}$ B lymphocytes (known as age-associated B cells or ABCs) to assess lupus nephritis; however, we also reported the finding of a related cell subset $CD11c^{+}$ T-bet^{+} $CD21^{hi}$ B cells that are almost absent when renal manifestations arise[22]. Importantly, this CD^{21hi} subset could be used as a prognostic factor as their numbers strongly correlate with a lower SLE activity. In addition, we found that either ABCs or CD^{21hi} B cell subsets could be considered to evaluate the response to induction therapy in LN[22].

CONCLUSIONS

Despite the large quantity of recently published data that have validated new serum markers for lupus nephritis (Table 1), several research groups keep working to identify novel molecules or cells that account for the diagnosis, prognosis, and management of these patients. We believe that exploratory efforts regarding serum biomarker searching should now be focused on generating prospective randomized high-scale clinical trials including patients with different ethnic backgrounds. These approaches will probably deliver schemes that include combining these novel LN markers with conventional clinical parameters to enhance sensitivity and specificity regarding the prediction of renal flares, staging, and therapeutical management of LN patients.

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REFERENCES

1. Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB. Type I interferon in the pathogenesis of systemic lupus erythematosus. Curr Opin Immunol. 2020;67:87-94.
2. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825-35.
3. Sada KE, Makino H. Usefulness of ISN/RPS classification of lupus nephritis. J Korean Med Sci. 2009;24 Suppl:S7-10.
4. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and bayesian meta-analysis. Arthritis Rheumatol. 2016;68:1432-41.
5. Morales E, Galindo M, Trujillo H, Praga M. Update on lupus nephritis: looking for a new vision. Nephron. 2021;145:1-13.
6. Capecchi R, Puxeddu I, Pratesi F, Migliorini P. New biomarkers in SLE: from bench to bedside. Rheumatology (Oxford). 2020; 59:v12-8.
7. Radin M, Miraglia P, Barinotti A, Fenoglio R, Roccatello D, Sciascia S. Prognostic and diagnostic values of novel serum and urine biomarkers in lupus nephritis: a systematic review. Am J Nephrol. 2021;52:559-71.
8. Ghafouri-Fard S, Shahir M, Taheri M, Salimi A. A review on the role of chemokines in the pathogenesis of systemic lupus erythematosus. Cytokine. 2021;146:155640.
9. Abozaid MA, Ahmed GH, Tawfik NM, Sayed SK, Ghandour AM, Madkour RA. Serum and Urine monocyte chemoattractant protein-1 as a markers for lupus nephritis. Egypt J Immunol. 2020; 27:97-107.
10. Bezalel S, Guri KM, Elbirt D, Asher I, Sthoeger ZM. Type I interferon signature in systemic lupus erythematosus. Isr Med Assoc J. 2014;16:246-9.
11. Graf M, von Stuckrad SL, Uruha A, Klotsche J, Zorn-Pauly L, Unterwalder N, et al. SIGLEC1 enables straightforward assessment of Type I interferon activity in idiopathic inflammatory myopathies. RMD Open. 2022;8:e001934.
12. Oliveira JJ, Karrar S, Rainbow DB, Pinder CL, Clarke P, Garcia AR, et al. The plasma biomarker soluble SIGLEC-1 is associated with the Type I interferon transcriptional signature, ethnic background and renal disease in systemic lupus erythematosus. Arthritis Res Ther. 2018;20:152.
13. Puapatanakul P, Chansritrakul S, Susantitaphong P, Ueaphongsukkit T, Eiam-Ong S, Praditpornsilpa K, et al. Interferon-inducible protein 10 and disease activity in systemic lupus erythematosus and lupus nephritis: a systematic review and meta-analysis. Int J Mol Sci. 2019;20:4954.
14. Matsuoka N, Fujita Y, Temmoku J, Furuya MY, Asano T, Sato S, et al. Galectin-9 as a biomarker for disease activity in systemic lupus erythematosus. PLoS One. 2020;15:e0227069.
15. Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. Front Immunol. 2013;4:289.
16. Xiang M, Feng Y, Wang Y, Wang J, Zhang Z, Liang J, et al. Correlation between circulating interleukin-18 level and systemic lupus erythematosus: a meta-analysis. Sci Rep. 2021;11:4707.
17. Migliorini P, Anzilotti C, Pratesi F, Quattroni P, Bargagna M, Dinarello CA, et al. Serum and urinary levels of IL-18 and its inhibitor IL-18BP in systemic lupus erythematosus. Eur Cytokine Netw. 2010;21:264-71.

18. Johnson NH, Keane RW, de Rivero Vaccari JP. Renal and inflammatory proteins as biomarkers of diabetic kidney disease and lupus nephritis. Oxid Med Cell Longev. 2022;2022:5631099.
19. Wardowska A, Komorniczak M, Skoniecka A, Bullo-Piontecka B, Lisowska KA, Debska-Slizien MA, et al. Alterations in peripheral blood B cells in systemic lupus erythematosus patients with renal insufficiency. Int Immunopharmacol. 2020;83:106451.
20. Dieudonne Y, Gies V, Guffroy A, Keime C, Bird AK, Liesveld J, et al. Transitional B cells in quiescent SLE: an early checkpoint imprinted by IFN. J Autoimmun. 2019;102:150-8.
21. Choi JY, Ho JH, Pasoto SG, Bunin V, Kim ST, Carrasco S, et al. Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity. Arthritis Rheumatol. 2015;67:988-99.
22. Sosa-Hernandez VA, Romero-Ramirez S, Cervantes-Diaz R, Carrillo-Vazquez DA, Navarro-Hernandez IC, Whittall-Garcia LP, et al. CD11c(+) T-bet(+) CD21(hi) B cells are negatively associated with renal impairment in systemic lupus erythematosus and act as a marker for nephritis remission. Front Immunol. 2022;13:892241.