Editorial

TWEAK: a novel biomarker for lupus nephritis?

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Abstract

Renal involvement is common in systemic lupus erythematosus. Early diagnosis of lupus nephritis (LN), allowing the instigation of appropriate therapy, remains an important clinical challenge. Current biomarkers in clinical practice are less than ideal, lacking both sensitivity and specificity. In the previous issue of *Arthritis Research & Therapy*, Schwartz and colleagues demonstrated the potential value of urinary TNF-like weak inducer of apoptosis (uTWEAK) as a biomarker for LN. They showed that uTWEAK is elevated in subjects with LN at diagnosis compared with those with systemic lupus erythematosus but no renal disease, and correlates with the degree of clinical disease activity. These data are thought-provoking and provide the platform for future longer-term studies.

In the previous issue of *Arthritis Research & Therapy*, Schwartz and colleagues demonstrated the potential value of urinary TNF-like weak inducer of apoptosis (uTWEAK) as a biomarker for lupus nephritis (LN) [1]. Renal involvement in systemic lupus erythematosus (SLE) is common – with ~50% of patients developing LN in the first year of diagnosis – and is associated with an adverse outcome [2]. Current immunosuppressive therapy for LN is often associated with significant side effects [3], and, despite treatment, some patients develop progressive renal injury resulting in end-stage renal disease. Furthermore, those patients who respond to treatment remain at risk of disease relapses.

Biomarkers are important in the management of LN and provide insights into the pathogenesis of disease. Current disease markers include serum C-reactive protein and complement levels, antibodies to double-stranded DNA and proteinuria. These markers, however, lack both sensitivity and specificity for LN. Furthermore, measurement of renal function using serum creatinine is often inadequate because substantial renal tissue damage can occur before function is impaired to a detectable extent [4]. Renal biopsy remains the gold standard for assessment of LN disease activity. Serial renal biopsies, however, are not appropriate in clinical practice. There is therefore an important unmet need for biomarkers that discriminate disease severity, assess response to therapy and more accurately predict disease relapses. These biomarkers would allow early implementation of appropriate treatments with the hope of preventing disease progression.

TNF-like weak inducer of apoptosis (TWEAK) is a multifunctional cytokine that is a member of the TNF superfamily and binds to its cognate receptor Fn14. It signals through the NF-κB pathway and can stimulate a wide array of cytokines, chemokines and cell adhesion molecules. TWEAK plays a role in tissue inflammation, repair and regeneration in many diseases, including SLE [5]. In a mouse model of SLE, the absence of Fn14 or treatment with an anti-TWEAK antibody reduces renal inflammation and severity of proteinuria [6]. Similarly, inhibition of TWEAK in models of multiple sclerosis, rheumatoid arthritis and ischaemic injury has anti-inflammatory effects [5].

In the current paper by Schwartz and colleagues, TWEAK was assessed as a biomarker for LN in both cross-sectional and longitudinal studies. In the former, uTWEAK was elevated in subjects with LN at diagnosis compared with those with SLE but no renal disease, and correlated with the degree of clinical disease activity as measured using a standard activity index. This distinction remained true when corrected for both renal function and SLE disease severity. Those patients with LN, however, had uTWEAK values that overlapped with those from SLE subjects without LN, as well

LN = lupus nephritis; NF = nuclear factor; SLE = systemic lupus erythematosus; TNF = tumour necrosis factor; TWEAK = TNF-like weak inducer of apoptosis; uTWEAK = urinary TNF-like weak inducer of apoptosis.

Table 1

Urinary biomarkers in lupus nephritis

Urinary marker	Function	Patient cohort	Main findings
Monocyte chemoattractant protein-1 (MCP-1) [7]	Chemokine, particularly for monocyte	25 adult patients with renal flare	Urinary MCP-1 predicted flare by 2 to 4 months and slowly fell following treatment
Neutrophil gelatinase-associated lipocalin (NGAL) [8]	Antimicrobial protein and siderophore	35 paediatric patients, 18 with renal disease	Urinary NGAL associated with renal disease and chronic damage (90% sensitivity). Not as strongly associated in adult patients
Hepcidin [9]	Antimicrobial protein and siderophore	19 adult patients with renal flares. Urine assessed using proteomics	Urinary hepcidin predicted flare by 4 months and reduced with treatment
Endothelin-1 (ET-1) [10]	Vasoconstrictor, with roles in inflammation and fibrosis	10 adult patients with lupus nephritis	Fractional excretion of ET-1 correlated with lupus nephritis and fell with treatment
TNF-like weak inducer of apoptosis (TWEAK) [1]	Proinflammatory cytokine. May be involved in resolution of injury	30 patients with lupus nephritis, 13 lupus nephritis patients in a longitudinal study	Urinary TWEAK correlated with lupus nephritis disease activity and fell with treatment

as those with rheumatoid arthritis, osteoarthritis and other non-inflammatory renal disease – suggesting the lack of specificity of uTWEAK for LN. Furthermore, all subjects studied had a good level of renal function (serum creatinine ~1 mg/dl), and so it remains unclear how uTWEAK may be affected by more significant declines in renal function. This may be important because the authors state that serum TWEAK did not show any of the associations described, suggesting that uTWEAK may be of renal origin. Unfortunately, uTWEAK did not discriminate between different LN histological classes. This is a common problem in LN biomarker studies. The problem probably relates to the small number of subjects studied who are then subgrouped into a number of histological classes, the inherent sampling error associated with renal biopsy, and the lack of a clear system to assess inflammatory disease activity at the tissue level. In the longitudinal study, uTWEAK levels peaked at time of diagnosis of a LN flare and fell with its treatment, taking 4 months to return to preflare levels. Unfortunately, the small rise in uTWEAK prior to the disease flare does not appear to have predictive value.

The work of Schwartz and colleagues complements a number of recent studies that have attempted to find new biomarkers for LN. In most of these studies the three main aims have been to assess the severity of renal inflammation, to monitor response to immunosuppressive therapy and to predict flare of disease. A number of promising candidates have been identified and these are summarised in Table 1. All of these potential biomarkers are more sensitive at identifying renal inflammation than the standard assays (serum creatinine, proteinuria, double-stranded DNA, complement). There remain, however, common weaknesses. No potential biomarkers have been correlated with the histological class of LN or the severity of tissue injury; as such, they cannot supplant repeat renal biopsies. None of the potential biomarkers are specific for LN, as they can be upregulated in other forms of renal inflammation and may increase as renal function declines. Finally, no long-term studies using large cohorts of LN patients have been performed.

It remains unlikely that a single urinary biomarker will provide sufficient information to determine diagnosis, response to therapy and disease activity in LN. The scene is now set, however, for studies in which multiple markers may be compared and correlated with LN histology, disease progression and recurrence. This research will become of increasing importance as treatment for LN becomes more tailored to the individual.

Competing interests

The authors declare that they have no competing interests.

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