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Editorial

**TWEAK: a novel biomarker for lupus nephritis?**

Neeraj Dhaun¹ and David C Kluth²

¹Clinical Pharmacology Unit, University of Edinburgh, The Queen’s Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK
²Centre for Inflammation Research, University of Edinburgh, The Queen’s Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK

Corresponding author: Neeraj Dhaun, bean.dhaun@ed.ac.uk

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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

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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.
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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