

## REVIEW

# Unmet medical needs in systemic lupus erythematosus

Aisha Lateef<sup>1</sup> and Michelle Petri<sup>\*2</sup>

### Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease of diverse manifestations, with onset usually in young women in the third to fourth decade of life. The chronic nature of this relapsing remitting disease leads to organ damage accrual over time. Mortality and morbidity are increased in patients with SLE compared with the general population. Therapeutic advances over the last few decades have led to significant improvements in patient outcomes. Five-year survival has improved to over 90% from a low of 50% in the 1950s. However, multiple aspects of the management of SLE patients are still far from optimal. Early diagnosis remains a challenge; diagnostic delays leading to delay in definitive treatment are common. Monitoring treatment remains problematic due to the paucity of sensitive biomarkers. Current treatment regimens rely heavily on corticosteroids, even though corticosteroids are well known to cause organ damage. Treatment of refractory disease manifestations such as nephritis, recalcitrant cutaneous lesions and neurological involvement require new approaches with greater efficacy. Cognitive dysfunction is common in SLE patients, but early recognition and adequate treatment are yet to be established. Premature accelerated atherosclerosis remains a leading cause of morbidity and mortality. Fatigue is one of the most disabling symptoms, and contributes to the poor quality of life in patients with SLE. Ongoing research in SLE faces many challenges, including enrollment of homogeneous patient populations, use of reliable outcome measures and a standard control arm. The current review will highlight some of the outstanding unmet challenges in the management of this complex disease.

### Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, predominantly affecting young women during the prime years of their life. The chronic nature of the disease, its relapsing remitting course and organ damage accrual over time frustrate both the physician and the patient. Clinical and translational research has advanced the available therapeutic options, translating into better patient outcomes. Five-year survival in patients with SLE has improved from 50% in the 1950s to over 90% currently. However, the mortality still remains high compared with the general population.

Multiple aspects of SLE remain challenging. The diverse and nonspecific presentations can lead to delay in diagnosis. Disease monitoring remains difficult due to the low sensitivity of current disease activity markers. Management of refractory disease, especially nephritis, cutaneous and neuropsychiatric manifestations, remains unsatisfactory. End-stage renal failure, scarring cutaneous lesions and neurological damage remain fearsome complications of the disease. Cardiovascular disease secondary to accelerated atherosclerosis has emerged as an important contributor to the higher morbidity and mortality in longstanding disease. Damage due to both disease and treatment, especially corticosteroid-associated damage, tends to accumulate over time. Fatigue, fibromyalgia and depression negatively impact the quality of life (QoL). Clinical research in the field of SLE therapeutics has met with limited success in recent years. Heterogeneous patient populations, limitations of outcome measures and the lack of a uniform control group are mostly responsible for the suboptimal responses.

Although there are numerous unmet medical needs in SLE, this review will focus on some of the major outstanding issues – including early diagnosis, biomarkers in SLE, management of refractory disease, atherosclerosis in SLE, corticosteroid-associated damage, QoL in SLE, and clinical research in SLE.

### Early diagnosis

SLE is a multi-system heterogeneous disease with protean manifestations. Initial nonspecific presentations can lead to diagnostic delays. The revised American College of

\*Correspondence: mpetri@jhmi.edu

<sup>2</sup>Division of Rheumatology, Johns Hopkins University, School of Medicine, Johns Hopkins Lupus Center, 1830 E. Monument Street, Suite 7500, Baltimore, MD 21205, USA

Full list of author information is available at the end of the article

Rheumatology (ACR) classification criteria, although not designed for diagnostic purposes, have been used by rheumatologists for almost three decades [1]. The Systemic Lupus International Collaborating Clinics (SLICC) group recently developed another set of revised criteria. These new criteria include 17 variables derived by expert consensus (SLICC committee members) and statistical analysis, using real-life patient scenarios. The final set of new criteria was then validated in another group of SLE patients and controls. The control group comprised other autoimmune diseases, which may have overlapping features with SLE.

SLICC criteria require that at least one clinical criterion and one immunologic criterion be present, with a total of four criteria, to have a classification of SLE. Under this new classification, lupus nephritis by biopsy (in the presence of SLE autoantibodies) is sufficient for classification [2]. Using expert consensus as the gold standard, the revised criteria demonstrated greater sensitivity (97% vs. 83%,  $P < 0.0001$ ) but less specificity (84% vs. 96%,  $P < 0.0001$ ) than the current ACR criteria in the validation group [2]. These criteria are clinically more relevant and will probably identify more patients with clinically defined lupus than using the current ACR criteria. However, one should stress that these criteria are primarily meant for classification of patient cohorts for research and their use for diagnostic purposes has to be carried out with caution. Some patients may initially present with insufficient features to fulfill the classification criteria, termed 'incomplete lupus' or 'lupus-like disease' by some groups.

### Biomarkers in systemic lupus erythematosus

SLE is the most diverse autoimmune disease, clinically and serologically. Genetic influences as well as epigenetic and environmental interactions probably play a role, perhaps dependent on the ethnic background of the individual. Classification criteria may help but currently, there is no single parameter that is sensitive or specific enough to correctly identify or subtype all SLE patients. Similarly, the disease course can be variable with either intermittent flares or chronic activity. Levels of autoantibodies (anti-double-stranded (DNA) antibody) and complement components represent serologic disease activity. They are routinely used to monitor disease activity in most clinical settings, but their association with clinical activity has not been consistent in longitudinal studies [3].

There is an unmet need for more sensitive and reliable biomarkers that can predict susceptibility, activity, severity and disease subtype in SLE. Multiple candidate markers have been proposed, including the type 1 interferon signature, B-lymphocyte stimulator and many others [4-13]. These markers are currently only a research

tool and not a single biomarker has been validated for clinical use to date. As SLE is a heterogeneous disease, a single biomarker is unlikely to be sufficient. Rather, different markers may provide information about specific disease aspects, as summarized in Table 1.

### Management of refractory disease

There is no clear definition of refractory disease in SLE, but it generally refers to patients who fail to respond to conventional treatments. In a heterogeneous disease such as SLE, the clinical situation may vary, depending on the disease manifestations and organ involvement. Although any clinical feature may become persistent and non-responsive to therapy, the most concerning features are refractory lupus nephritis, scarring cutaneous disease and neuropsychiatric lupus (NPSLE).

### Lupus nephritis

Renal involvement is a major cause of mortality and morbidity in SLE. A large proportion of patients, up to 60%, develop immune complex-mediated lupus nephritis during the course of their disease. The treatment of lupus nephritis has rapidly advanced over the last few decades. Glucocorticoids and cyclophosphamide were once considered the standard of care. Although effective in the majority of patients, cyclophosphamide was associated with serious adverse effects including infections, malignancy and infertility. Lower doses of cyclophosphamide and mycophenolate emerged as effective options for induction therapy, with better safety profiles [14,15]. Patients with different ethnic backgrounds might have differential responses to cyclophosphamide versus mycophenolate [16]. Azathioprine and mycophenolate have been shown to be effective options for maintenance therapy in randomized trials [17,18]. Mycophenolate was superior to azathioprine in the ALMS trial, but not in a MAINTAIN trial [17,18].

Alternate approaches have been tried for patients failing to respond to these conventional treatments. Calcineurin inhibitors, cyclosporine and recently tacrolimus have shown promising results in patients unresponsive to first-line therapies, but need further evaluation in larger controlled trials [19-21]. B cells play a central role in the pathogenesis of lupus nephritis, making them a logical therapeutic target. Rituximab, a chimeric anti-CD20 antibody, efficiently and reliably depletes CD20-positive B cells. A large number of open-label studies documented the efficacy of rituximab in refractory lupus nephritis [22]. Unfortunately, a large randomized controlled trial (LUNAR) did not show any significant differences in outcomes with rituximab compared with placebo [23]. However, this trial excluded patients with refractory disease, the very subset in which evidence of benefit was shown in open-label studies. Additionally,

**Table 1. Potential biomarkers and their proposed applications in SLE**

Category	Biomarker	Associations	Comments
Susceptibility	IRF-5	Specific haplotypes confer increased susceptibility to SLE. Genome-wide association studies have identified many loci, mostly related to immune regulatory genes	Genetic epistasis between different loci has been described
	STAT-4		
Disease activity	HLA-DRB1	High levels of IFN $\alpha$ or IFN inducible genes (IFN signature) and chemokines correlated with disease activity	Despite the association with activity, the IFN signature was not predictive of flare in longitudinal studies
	PTPN22		
	Fc $\gamma$ receptors		
Disease severity	Complement proteins	Deficiency in early components of the classical complement pathway is a strong risk factor for SLE	Partial C4 deficiency due to gene copy number variations increases the risk of SLE
	IFN $\alpha$	High levels of IFN $\alpha$ or IFN inducible genes (IFN signature) and chemokines correlated with disease activity	Despite the association with activity, the IFN signature was not predictive of flare in longitudinal studies
	B-cell subsets	CD27 <sup>high</sup> plasma cells correlated with disease activity	
Disease subtype	Serum cytokines, receptors and adhesion molecules	Multiple cytokines (for example, IL-6, IL-10, IL-16, IL-18), soluble receptors (sIL-2 R) and adhesion molecules (for example, sICAM and sVCAM) have been suggested to correlate with disease activity	Data are limited and almost all proposed candidates are still far from being established as a reliable marker in SLE
	IFN $\alpha$	High IFN signature group has more severe disease manifestations	Holds the potential to identify high-risk patients
Flares	IFN $\alpha$	High versus low IFN groups have distinct clinical features, autoantibody associations and genetic profiles	IFN signature and BlyS levels may potentially define subgroups of patients
	BlyS	High BlyS levels are associated with specific autoantibodies	
Organ specific	BlyS	Higher and rising BlyS levels were predictive of increase in disease activity at subsequent visit	The association has not been consistent across the studies
	Anti-C1-q antibodies	Correlate with the presence and severity of lupus nephritis	Potential robust marker for lupus nephritis
	Anti-NR2 antibodies	Associated with neuropsychiatric manifestations in a murine model	Human results have been largely negative

Anti NR2 antibodies, anti-N-methyl-D-aspartate (NMDA) receptor antibodies; BlyS, B-lymphocyte stimulator; HLA, human leukocyte antigen; IFN, interferon; IRF, interferon regulatory factor; PTPN22, protein tyrosine phosphatase N22; sICAM, soluble intracellular adhesion molecule; SLE, systemic lupus erythematosus; STAT, signal transduction and activator of transcription; sVCAM, soluble vascular adhesion molecule.

heavy background immunosuppression may have masked any beneficial effect of rituximab [24]. Open-label data continue to be positive and a recent systematic review concluded that evidence for rituximab efficacy in refractory lupus nephritis is strong, and another well-conducted trial may provide more answers [25,26].

Hydroxychloroquine deserves special mention in the treatment of SLE, including lupus nephritis. Hydroxychloroquine has been shown to improve response rates, decrease flares and improve survival [27,28]. Every SLE patient should receive hydroxychloroquine, unless intolerant or contraindicated. Renal protective therapies such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, strict control of blood pressure and serum lipids, are important adjuncts to therapeutic regimens for lupus nephritis [29,30].

Despite aggressive immunosuppressive and supportive therapies, induction of remission may be slow or partial,

relapses remain common and progression to renal damage may occur. The incidence of end-stage renal disease attributable to lupus nephritis has not declined over the decades [31,32]. About 10 to 30% of SLE patients still progress to end-stage renal disease with associated morbidity and mortality. Multiple variables affect renal prognosis, including the disease severity, antibody associations, ethnicity, genetic background, socioeconomic status and concomitant co-morbidities [33,34].

#### Cutaneous lupus

Skin involvement occurs in 70 to 85% of SLE patients and includes acute, subacute and chronic cutaneous lesions. Discoid lupus is the most common form of chronic lesion, and may be the initial presentation of SLE in up to 10% of cases. Resistant discoid lesions may cause scarring of the affected skin areas and permanent scarring alopecia. This can lead to significant disfigurement,

emotional distress, physical limitations and disability in a large number of patients. Although generally believed to be associated with less severe systemic disease, discoid lupus has also been associated with more damage accrual [35]. In addition, the risk of squamous cell carcinoma is increased in scarred areas.

The conventional approaches include photoprotection, corticosteroids (topical, intralesional and systemic) and antimalarial agents [36]. Other topical agents such as calcineurin inhibitors and retinoids can benefit some patients with refractory lesions. Multiple immunosuppressants including methotrexate, azathioprine, mycophenolate, cyclophosphamide, dapsone, gold and thalidomide have been tried for refractory disease [36]. Biologic agents including TNF inhibitors, efazulimab (anti-CD11 antibody) rituximab (anti-CD20 antibody) and tocilizumab (anti-IL-6) have been used in some refractory cases [37]. Data are limited to anecdotal reports, case series and open studies. A recent Cochrane review concluded that the evidence about therapies for discoid lupus, other than topical corticosteroids and anti-malarials, was not conclusive [38]. The need for additional therapies for such a disfiguring manifestation of young people with SLE cannot be overemphasized.

#### Neuropsychiatric lupus

NPSLE remains one of the most challenging issues in the management of SLE patients. Affecting up to 30 to 40% of the patients, NPSLE includes diverse neurologic and psychiatric manifestations, from subtle cognitive deficits to severe psychosis, seizures and strokes. The attribution of neuropsychiatric events to SLE is often challenging in the clinical setting. The ACR committee has described case definitions for 19 NPSLE syndromes, but the specificity remains low [39,40]. Anti-ribosomal P antibodies have been associated with NPSLE, especially psychosis [41]. Measurement of cerebral spinal fluid cytokine and chemokine levels remains a research tool [42]. Neuro-imaging can be helpful but the sensitivity and specificity remain quite low [43].

The management of NPSLE depends on the manifestation and the likely predominant mechanism. Current strategies include the use of immunosuppressive therapies when the underlying mechanisms are predominantly inflammatory. Anticoagulation and/or antiplatelet therapy should be considered when antiphospholipid antibodies are persistently positive in moderate to high titers. Non-SLE precipitation and aggravating factors should be addressed. Cognitive dysfunction merits special mention. It is present in a majority of SLE patients, even newly diagnosed patients [44,45], and has also been associated with psychosocial factors such as depression, fatigue, anxiety and pain [45,46]. Although antidepressants may benefit some patients with depression and

cognitive dysfunction, no treatment of proven benefit exists for cognitive dysfunction in SLE [45,47].

NPSLE management remains problematic due to the lack of specific tools for diagnosis and attribution. Treatment options are limited to glucocorticoids and a few immunosuppressants (cyclophosphamide, azathioprine, mycophenolate, rituximab), with efficacy mostly suggested by case reports and open-label studies. A European League Against Rheumatism task force recently published recommendations on the management of NPSLE; it was felt that 'there is currently no good quality evidence to guide several diagnostic, primary prevention, therapeutic and monitoring decisions in NPSLE, emphasizing the need for further research' [48].

#### Atherosclerosis and systemic lupus erythematosus

SLE is associated with premature and accelerated atherosclerosis, contributing significantly to the increased mortality and morbidity associated with the disease [49].

An increased frequency of conventional risk factors, such as hypertension, dyslipidemia and diabetes, has been noted in patients with SLE. Yet the excess risk cannot be fully explained by the traditional Framingham risk factors [50,51].

Multiple putative mechanisms have been proposed but the exact pathogenesis of atherosclerosis in the setting of SLE is yet to be fully elucidated. High-density lipoprotein was reported to be significantly dysfunctional and pro-inflammatory in SLE patients, and correlated with measures of subclinical atherosclerosis [52]. Endothelial cell dysfunction in SLE leads to abnormal vascular reactivity and repair, contributing to the accelerated atherogenesis [53]. Interferon activity was independently associated with subclinical measures of atherosclerosis in a cohort study [54]. Specific subtypes of peripheral blood mononuclear cells, the low-density granulocytes, and increased Toll-like receptor signaling have been proposed to contribute to higher interferon production and vascular dysfunction in patients with SLE [55,56]. Autoantibodies including antiphospholipid and antilipoprotein antibodies have been associated with abnormal vascular function and atherosclerosis in SLE [57].

Despite the evidence of a link between inflammation and atherosclerosis in SLE, multiple studies have failed to show any consistent association of coronary calcium scores or carotid plaques with markers of disease activity [51,58,59].

In patients with SLE, the proportion of noncalcified vulnerable plaque was shown to be increased compared with the calcified stable plaque, and correlated with measures of disease activity [60]. Elevated homocysteine, asymmetric dimethylarginine, leptin and high-sensitivity C-reactive protein levels have been proposed as markers of accelerated atherosclerosis in SLE in some studies [61-64].

The management of atherosclerosis in SLE is currently limited to the control of traditional risk factors. Statins are believed to have anti-inflammatory properties, in addition to their lipid-lowering effects. However, two large randomized controlled trials failed to show any beneficial effects of 20 mg atorvastatin versus placebo in adult and pediatric SLE patients without clinical cardiovascular disease [65,66]. **The use of statins in SLE patients should thus be limited to treat hyperlipidemia.** Hydroxychloroquine was noted to have weak protective effects on cardiovascular risk in SLE [28]. Mycophenolate reduced the atherosclerotic burden in mice models but failed to reduce progression of subclinical atherosclerosis in a large cohort study [67,68]. Several trials evaluating anti-interferon therapy in SLE are currently ongoing, and beneficial effects on atherosclerosis might become evident. However, no SLE treatment is currently of proven benefit to reduce the risk of or halt the progression of atherosclerosis in SLE.

### **Corticosteroid-associated damage in systemic lupus erythematosus**

Corticosteroids are the mainstay of therapy for SLE, with proven efficacy. The harm they cause in the short term and the long term, however, is one of the major issues in SLE management. Corticosteroids increase the traditional cardiovascular risk factors, including serum lipids, blood pressure, weight and glucose. Fifteen years after the diagnosis of SLE, the majority of permanent organ damage can be attributed to the corticosteroids. Although the risk of damage is higher with high doses, there is no safe dose for chronic use. Even small doses, if continued long enough, will significantly increase the morbidity [69]. The cumulative dose of corticosteroids has significant association with cataracts and osteoporotic fractures. Both the current dose and the cumulative dose are associated with cardiovascular events [70]. When adjusted for confounding by indication due to SLE disease activity, the hazard ratio for organ damage increases dramatically with prednisone doses of 6 to 12 mg/day (hazard ratio = 1.5), 12 to 18 mg/day (hazard ratio = 1.64) and >18 mg/day (hazard ratio = 2.51) [69]. Every attempt should be made to minimize the dose and duration of corticosteroid exposure.

### **Quality of life in systemic lupus erythematosus**

The QoL in patients with SLE is significantly lower than in healthy controls and patients with other chronic diseases [71,72]. Disease activity and organ damage did not consistently correlate with lower QoL in SLE. Instead, the major predictors of poor QoL in SLE are nondisease-specific variables including fatigue, chronic pain and mood disturbances [71,72].

Fatigue is a common and often crippling symptom experienced by about 85 to 92% of patients with SLE,

with 50% rating it as the most disabling symptom [73]. Fatigue can significantly contribute to the poor QoL in SLE patients [72]. The pathophysiological mechanisms of SLE-related fatigue are probably multifactorial, with a predominant role being played by the psychological domains. Psychosocial factors such as mood disorders, anxiety, poor sleep quality and chronic pain syndrome have shown consistent associations with fatigue in SLE [74,75]. Exercise programs have been shown to have a positive impact on fatigue among SLE patients [76]. However, fatigue remains an unmet need, reflected by the finding that 81% of SLE patients feel that the healthcare service did not support them enough in the management of SLE-related fatigue [77].

Fibromyalgia is a chronic pain disorder characterized by widespread generalized pain, often associated with fatigue, anxiety and sleep disturbances. The prevalence of fibromyalgia is much higher in SLE patients, compared with the general population [78]. Fibromyalgia in SLE contributes to the lower QoL and correlates with psychosomatic and affective variables but not with disease activity or damage [78-80]. The widespread pain of concomitant fibromyalgia can lead to diagnostic confusions and potential overtreatment if symptoms are mistaken for SLE disease activity.

Mood disturbances are very common in patients with SLE, with depression being the most prevalent affective symptom [81,82]. Depression contributes to the fatigue and cognitive dysfunction, and significantly correlates with lower QoL in patients with SLE [45,71,83]. Although psychological effects of dealing with a chronic disease may contribute to the high prevalence of depression, disease-specific mechanisms probably play a role. Associations with specific antibodies and alterations in cerebral blood flow have been reported in depressed SLE patients [84,85]. However, the data are not conclusive and depression in patients with SLE should be treated with conventional measures similar to the general population.

### **Perspective on future therapeutics and clinical research in SLE**

Despite advances in therapies, the control of disease activity in SLE remains suboptimal. **Flares are common and sustained disease control is generally limited to a small fraction of patients** [86]. These findings suggest that, despite significant improvements in SLE treatment, conventional approaches have probably reached their maximal benefit and alternate options have to be considered. Multiple new agents with immunomodulatory effects have been investigated in recent years but limited success has been achieved. Two large randomized controlled trials evaluating rituximab for treatment of SLE failed to meet their primary endpoints, despite good

efficacy data in open-label studies [23,87]. Only belimumab showed efficacy in randomized controlled trials and received US Food and Drug Administration approval for treatment of SLE [88,89]. These studies have raised important issues that should be addressed in future SLE research.

The heterogeneous nature of the disease makes it difficult to design clinical studies in SLE. In the absence of specific biomarkers, classification criteria are generally used to define study populations. Although these criteria encompass the breadth of the disease spectrum, patients with diverse manifestations and probably different pathogenic mechanisms will be grouped together. This limitation can be avoided by defining specific disease subgroups based on organ manifestations, such as renal disease. However, this would seriously limit the eligible patient population, however, stressing the need for multicenter collaborative projects. Limiting the inclusion in this manner may not be even a viable option if uncommon manifestations are considered. Currently, some degree of heterogeneity in study populations has to be accepted.

Another major issue in SLE research has been the choice of outcome measures. The US Food and Drug Administration draft guidance statement on SLE clinical trials suggested the use of disease activity indices to measure the efficacy of the intended intervention [90]. Several such indices have been developed and validated for use in clinical trials. Some disease activity indices – such as the SLE Disease Activity Index (SLEDAI) and its variants (SLEDAI-2K, SELENA-SLEDAI) – measure overall disease activity, while others – such as the British Isles Lupus Assessment Group Index (BILAG) – measure organ-specific activity. Physician's global assessment uses the treating physician's overall assessment to assign a numerical value to the disease activity on a visual analog scale of 0 to 3 [91]. This assessment has been used to define flares (>1 point rise) in clinical trials [91]. Physician visual analog scale rating was found to have high variability in a comparative study of outcome measures by the SLICC study group [92], but it has been successfully incorporated as part of the SLE Responder Index (SRI) [93]. The SLE Responder Index is a composite index developed to incorporate the strengths of different disease activity indices. This index provides a comprehensive definition of meaningful clinical response and has been used to define the primary end point in clinical trials [93]. The SLE Responder Index utilizes the SELENA-SLEDAI score to determine global improvement, British Isles Lupus Assessment Group Index domain scores to ensure no significant worsening in previously unaffected organ systems, and physician's global assessment to ensure that improvements in disease activity are not achieved at the expense of the patient's

overall condition [93]. The SLE Responder Index has been used successfully in the belimumab phase 3 trials and has the potential to serve as an outcome measure in the future SLE therapeutic trials.

The background immunosuppression used as the standard of care in SLE trials adds another confounder to the picture. Most studies have employed diverse background treatments in both the treatment and placebo groups, to which the candidate agent is added. In addition, treatment adjustments have been either mandated or at least allowed during the studies. However, these concomitant therapies may have their own effects, masking the efficacy of the target intervention. Examples include the failed LUNAR and EXPLORER trials, in which rituximab or placebo were added to background therapy including high-dose corticosteroids and immunosuppressive drugs such as mycophenolate [23,87]. Efficacy of rituximab over placebo was not found in these trials, despite a large body of evidence favoring rituximab in observational and cohort studies. In contrast, the belimumab trial design permitted early tapering of corticosteroids and may have contributed, at least partially, to the positive results [88,89]. However, designing a trial in SLE where the active arm receives only the experimental agent will be difficult and unethical. There is a need to develop a clearly defined standard of care control arm, against which the newer agents can be tested.

The field of SLE clinical and therapeutic research is advancing rapidly. Large international collaborations have resulted in development of new criteria, composite outcome indices and insights into disease pathogenesis. Multiple newer biologic agents targeting specific immune system pathways and effectors are undergoing evaluation [94]. Hopefully, these efforts will lead to development of newer therapeutic agents in SLE, a dire need.

## Conclusions

The management of SLE remains a challenge despite significant advances in the treatment. The new SLICC classification criteria with better sensitivity will probably help in better identification of patients, but we have not yet reached the stage where early diagnosis can be universally achieved. The field of disease biomarkers is rapidly evolving with many putative candidates. However, no biomarker has been successfully validated for use in the routine clinical setting. Instead of a single measure, a battery of markers may perhaps be developed in the future to predict different disease aspects in a heterogeneous disease such as SLE. Refractory disease manifestations and development of damage associated with disease and therapies remain outstanding issues. Premature mortality and higher morbidity from atherosclerosis in this predominantly young group of

patients are a major concern. Fatigue is one of the most prevalent and disabling symptom in SLE, significantly contributing to the poor QoL. The quest for newer targeted therapies has met with limited success despite many clinical trials. Whether there is a true lack of efficacy or whether the trial designs in SLE are partly to blame is open to discussion. However, advances have been made in developing reliable outcome measures for clinical research. Future research will focus on the goals of increasing survival, limiting organ damage and improving QoL for patients with SLE.

#### Abbreviations

ACR, American College of Rheumatology; IL, interleukin; NPSLE, neuropsychiatric lupus; QoL, quality of life; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics; TNF, tumor necrosis factor.

#### Competing interests

The authors declare that they have no competing interests.

#### Declarations

This article has been published as part of *Arthritis Research & Therapy* Volume 14 Suppl 4, 2012: New therapeutic targets in systemic lupus erythematosus. The supplement was proposed and developed by the journal. Articles were commissioned by the journal, were independently prepared by the authors and have undergone the journal's standard peer review process. Publication of the supplement has been supported by an unrestricted educational grant from UCB. Completed articles underwent a data quality check by Darwin Healthcare Communications, funded by UCB

#### Author details

<sup>1</sup>Division of Rheumatology, University Medicine Cluster, National University Health System, 1E Kent Ridge Road, Singapore 119074, Singapore. <sup>2</sup>Division of Rheumatology, Johns Hopkins University, School of Medicine, Johns Hopkins Lupus Center, 1830 E. Monument Street, Suite 7500, Baltimore, MD 21205, USA.

Published: 18 December 2012

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doi:10.1186/ar3919

Cite this article as: Lateef A, Petri M: **Unmet medical needs in systemic lupus erythematosus.** *Arthritis Research & Therapy* 2012, **14**(Suppl 4):S4.