Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organ systems. In the past 40 years, prognosis for patients with SLE has improved significantly because of advances in the understanding of molecular mechanisms involved in the pathogenesis of disease, which has translated into early diagnosis and novel therapeutic strategies. This article will focus on three aspects that have shaped this transformation, namely; a revisit to diagnostic criteria, development of newer biomarkers, and incorporation of newer targeted therapies.

Classification Criteria of SLE

Pitfalls in existing criteria for SLE

Criteria for SLE classification was developed by the American College of Rheumatology (ACR) in 1971, and revised in 1982 and 1997.[1] These criteria were not weighted for specificity, sensitivity or disease severity, and often excluded patients with early or limited disease. In fact, data from tertiary centres suggested that only 60% of patients referred for SLE fulfilled the ACR criteria, whereas another 15% of patients had SLE features but did not fulfill the criteria.[2] The major pitfalls with ACR criteria, which created the need for newer criteria,[3] included the following.

- The 1982 criteria were biased and weighted toward cutaneous lupus, with four cutaneous criteria. However, the newer therapies for SLE were largely directed against renal or other major organ involvement.
- Hypocomplementemia (omitted in the 1982 criteria) has been shown to be strongly associated with SLE, and its exclusion from SLE criteria often missed patients with SLE.
- Advances have been made in autoantibody assays, such as the anti-phospholipid, anti-dsDNA, and anti-Sm antibodies. The criterion for anti-phospholipid antibodies has not been subjected to validation, and its inclusion may lead to confusion between SLE and primary APS. The appropriateness of new commercial enzyme-linked immunosorbent assay (ELISA) for anti-DNA has not been evaluated.

Keywords: Advances, connective tissue disorder, systemic lupus erythematosus

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• Many of the existing criteria require redefinition and refinement based on current practice. This is especially relevant for the renal and neurologic criteria (only psychosis and seizure are included) to reflect the breadth of neurologic lupus, as noted by the ACR neurologic classification criteria.[4]
• Future criteria must be generalizable to multiple ethnic groups and be internationally valid. Different frequencies of individual criteria for different ethnicities have already been shown for African-Americans and for Japanese.
• Future criteria need to include input from non-rheumatology specialists who frequently care for and diagnose lupus, including dermatologists, neurologists, and nephrologists.

SLE is likely a disease with multiple subsets. Accurate classification criteria would allow future clinical trials to look at treatment variability by subset, including chronic cutaneous lupus and APS.

SLICC criteria
This created the way for the “Systemic Lupus International Collaborating Clinics (SLICC) Classification 2012 Criteria.” SLICC group is an international group of investigators dedicated to SLE clinical research. The SLICC classification criteria for SLE represent an 8-year effort of clinical review, consensus, and statistical analyses. The new criteria are simple, include most SLE patients, and retain specificity while being more sensitive.

The final criteria were derived using recursive partitioning[5] (“tree-based” approach) (using the CART software package), in which patients were categorized into two groups based on all candidate variables, and the resulting partitions were evaluated. A simple rule was applied — the patient must satisfy at least four criteria, including at least one clinical criterion and one immunologic criterion; or the patient must have biopsy-proven lupus nephritis compatible with SLE and with ANA or anti-dsDNA antibodies. The SLICC classification criteria were subjected to rigorous testing. The new patient sample used for validation consisted of 690 patients and included patients from multiple centers with multiple diagnoses that have clinical features, which overlap with the clinical features of lupus.

The key features in SLICC criteria are that lupus nephritis alone with ANA positivity can be classified as SLE. Hypocomplementemia becomes an important component and multiple neurological syndromes like myelitis and mononeuritis multiplex have been included. The new SLICC criteria has a sensitivity and specificity of 94% and 92% compared to ACR criteria having 86% and 93%, respectively.

*Classify a patient as having SLE if*
• The patient satisfies four of the criteria (listed in Table 1) including at least one clinical criterion and one immunologic criterion; or
• The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.

Biomarkers In SLE
Biomarkers are very useful in diagnosis, evaluation, and management of SLE and can be of help in early detection of a disease flare and monitoring disease activity. An ideal biomarker should accurately detect disease activity and guide therapy at every stage of SLE.

Need for novel biomarkers
Autoantibodies like ANA and dsDNA have been the traditional agents used in the diagnosis of SLE. But ANA has a low specificity for SLE, and its sensitivity may be as low as 70%, especially early in the disease.[6] Anti-dsDNA is better with 95% specificity but has a low sensitivity.[7] This created the need for novel biomarkers for SLE. Decades of extensive work has led to discovery of a number of candidate biomarkers, the precise clinical utility of which-outside of the research setting-awaits determination.[8]

New biomarkers in SLE
The newer biomarkers developed for use in SLE are given in Table 2.[9] Anti-nucleosome antibodies are associated with organic damage and are useful in diagnosis of SLE, drug-induced lupus, disease flares, and early detection of lupus nephritis.[10] Anti-C-1q antibodies, NMDA receptor antibody, and anti-alpha actinin antibody have also shown promise in early diagnosis of SLE and diagnosis of flares. Numerous biomarkers have been investigated in lupus nephritis and have shown a role in early detection of renal pathology, predicting flares, and predicting chronic kidney disease as given in Tables 2 and 3.

Alternative biomarkers
New high-throughput technologies, such as transcriptomics and proteomics, have been applied in search for biomarkers. Interferon-signature gene
expression correlates with autoantibody profiles in SLE and may be useful in cutaneous lupus, discoid lupus, and neuromyelitis optica. Micro RNAs (MiRNAs) play a crucial role in maintaining immune system development and function, and are implicated in SLE. Unique miRNA expression signatures in SLE have the potential to not only act as biomarkers for the diagnosis and assessment of SLE but may be the future therapeutic potential in management of SLE. RNA microarray analyses of peripheral blood leukocytes can distinguish between SLE flare and infection and might be useful in the diagnosis and monitoring of the disease.

**Future insights — SLE biomarkers**

**Next-generation SLE biomarkers**

The focus today is shifting towards discovering biomarkers that predict onset of SLE in susceptible individuals, development of flares in patients with established SLE, predicting disease outcomes, and assessing the effectiveness of therapeutic interventions. These will allow proactive institution of therapeutic and even preventive strategies so that the therapeutic efficacy can be enhanced while treatment-related side effects can be minimized.

**Pharmacodynamic biomarkers**

New biomarkers are being searched to aid identification of patients who might respond favorably to a particular biologic, selection of the type and dose of biologics used, and evaluation of therapeutic efficacy. An illustrative example is sifalimumab and rontalizumab, anti-IFNα monoclonal antibodies under evaluation for the treatment of SLE, which were developed based on the seminal discovery of the interferon signature and related biomarkers.

**Treatment of SLE**

**Conventional therapies**

Early diagnosis and better treatment options of SLE and its complications have markedly improved the 5-year survival of patients with SLE. However, morbidity, especially renal failure, and mortality from cardiovascular events after long-term follow up are
Table 2: Novel biomarkers in diagnosis of SLE[11]

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Used As marker of</th>
<th>Role in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>New antibodies</td>
<td></td>
<td></td>
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<tr>
<td>Anti-nucleosome antibodies[12]</td>
<td>Disease activity</td>
<td>Drug-induced lupus</td>
</tr>
<tr>
<td></td>
<td>and organ involvement</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lupus flares</td>
</tr>
<tr>
<td>Anti-C1q antibodies[13]</td>
<td>Disease activity</td>
<td>Nephritic flares</td>
</tr>
<tr>
<td></td>
<td>and organ involvement</td>
<td>Negative predictive value of 100%</td>
</tr>
<tr>
<td>Anti-platelet antibodies</td>
<td>Platelets</td>
<td>Thrombocytopenia with lupus</td>
</tr>
<tr>
<td>NMDA receptor antibody[14]</td>
<td>Neuronal damage</td>
<td>Neuropsychiatric disease</td>
</tr>
<tr>
<td>Anti-Alpha actinin antibody[15]</td>
<td></td>
<td></td>
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<tr>
<td>Cellular markers/new molecules</td>
<td></td>
<td></td>
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<tr>
<td>CD27 plasma cells[16]</td>
<td>Disease activity</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>CD44v3/CD44v6 - T cells[17]</td>
<td>Disease activity</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>CD4-CD8- (double negative) T cells[18]</td>
<td>Disease activity</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>Plasma MBL[19]</td>
<td>Disease activity</td>
<td>Lupus nephritis (high levels)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous lupus (low levels)</td>
</tr>
<tr>
<td>Complement Activation products[20]</td>
<td>Diagnosis or disease activity</td>
<td>Diagnosis of SLE</td>
</tr>
<tr>
<td>[C4d-bound RBCs, anti-MCV, EC4d, and BC4d]</td>
<td></td>
<td></td>
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<tr>
<td>Cytokines[21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-α, IFN-γ[22]</td>
<td>Disease activity/</td>
<td>Marker and potential predictive Marker for anti-type I IFN therapy</td>
</tr>
<tr>
<td></td>
<td>flares</td>
<td></td>
</tr>
<tr>
<td>MCP-1[23]</td>
<td>Disease activity/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>flares</td>
<td></td>
</tr>
<tr>
<td>IL-2, IL-6, IL-10, IL-17, IL-23, TGF-B</td>
<td>Disease activity</td>
<td>Diagnosis and prognosis of SLE</td>
</tr>
<tr>
<td>TWEAK[23]</td>
<td>Disease activity</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>Genomic markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe receptor gene polymorphisms[24]</td>
<td>Disease susceptibility</td>
<td>Diagnosis of SLE</td>
</tr>
<tr>
<td>DNA Methylation markers (CD70, CD154, Perforin)[25]</td>
<td>Disease activity</td>
<td>Diagnosis and monitoring</td>
</tr>
<tr>
<td>Micro RNAs[26]</td>
<td>Disease activity</td>
<td>Monitoring of SLE</td>
</tr>
<tr>
<td></td>
<td>and effects of treatment</td>
<td>New gene therapy strategies</td>
</tr>
</tbody>
</table>

Table 3: Novel Biomarkers in Lupus Nephritis[27,28]

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predict Renal pathology</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Glycoprotein pathology</td>
<td></td>
</tr>
<tr>
<td>CXCL 10</td>
<td>Urine mRNA</td>
</tr>
<tr>
<td>CD 29</td>
<td>T cell surface markers</td>
</tr>
<tr>
<td>Anti-nucleosome antibody</td>
<td>Serum marker</td>
</tr>
<tr>
<td>Complement C4d</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Predict CKD</td>
<td></td>
</tr>
<tr>
<td>LFAFB</td>
<td>Urine protein</td>
</tr>
<tr>
<td>M EPCR</td>
<td>Endothelial surface marker</td>
</tr>
<tr>
<td>FOXP3</td>
<td>Urine mRNA</td>
</tr>
<tr>
<td>Predict Impending Nephritis Flare</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>Urine protein/ mRNA</td>
</tr>
<tr>
<td>NGAL</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Anti-αC1Q</td>
<td>Urine protein</td>
</tr>
<tr>
<td>α1-acid glycoprotein (AGP)</td>
<td>Urine protein</td>
</tr>
<tr>
<td>Mannose binding lectin</td>
<td>Serum protein</td>
</tr>
</tbody>
</table>

which has led to promising new leads in SLE therapy. Hydroxychloroquine acts by reducing the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells, processing and transport of the peptide-MHC complex to the cell membrane and results in down-regulation of the immune response against autoantigenic peptides.[31] Studies have shown that hydroxychloroquine is an essential medication in lupus nephritis, neuro lupus and has got a role in alleviating cutaneous, articular and other manifestations of SLE.[34] The benefits also include a favorable effect on lipid profile, lower side effects and a protection against the occurrence of thrombotic events.[35] Its efficiency has also been demonstrated in the reduction of the risk of flares and to have a protective effect on survival in people with SLE.[36]

**Targeted Therapy In SLE**

**Principle of targeted therapy**

B lymphocytes play a central role in the pathogenesis of SLE. Pathogenic autoantibodies produced by B cells leads to tissue damage via immune complex formation, complement activation, and direct effects on cells. They also contribute to immune dysregulation by producing cytokines, presenting antigens, and regulating T-cell functions.[37] The regulatory and effector functions of T cells are also abnormal in patients with SLE. Elevated levels of certain cytokines / chemokines / growth factors made by monocytes / macrophages and endothelial cells also drive lupus disease activity and organ damage. These include B-cell activating factor still an important issue. With the use of conventional therapies like corticosteroids, anti-malarials, aspirin, and hydroxychloroquine, half of patients with organ-threatening disease do not survive 20 years after diagnosis, and the quality of life for those individuals with all forms of SLE is usually seriously compromised.[32]

Thus, there is a need for improved therapies for SLE,
rituximab with methyl prednisolone (500 mg) on days 1 and 15 and maintenance treatment of mycophenolate mofetil. The study showed that about 90% of patients achieved complete remission in this regimen creating a ray of hope that oral steroids can be safely avoided in lupus nephritis with the use of rituximab.

The dosage of RTX may vary from low doses (100 mg weekly) used in thrombocytopenia of lupus to high

### Table 4: Targeted Therapies in SLE[^51]

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Role in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B Cell targeted therapies</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| B Cell depletion       | **Anti-CD 20**               | Rituximab: a. Effective in treating refractory SLE  
                        |                                                                             | b. Improvements in disease activity  
                        |                                                                             | c. No benefit in proliferative lupus nephritis |
|                        | **Anti-CD 22**               | Epratuzumab: a. Reduction in corticosteroid doses in SLE                     |
|                        | **Anti-CD 11**               | Efalizumab: Improvement in cutaneous SLE                                     |
| B Cell activation      | **Anti-B Lys Antibody**      | Belimumab: a. Reduction in SLE activity  
                        |                                                                             | b. Reduced flares                                                        |
| T-Cell target and costimulatory blockers | **Anti-CD40 ligand antibodies** | IDEC-131 (Toralizumab): Unproven role                                      |
|                        | **CTLA4-Ig Fusion protein**  | Abatacept: Improvements in non-life-threatening SLE manifestations          |
|                        | **Cell surface receptor activation inhibition** | Sirolimus: Role in Refractory SLE                                           |
|                        | **Cytokine inhibition**      |                                                                             |
|                        | **Anti-TNF-α**               | Infliximab: Doubtful efficacy in lupus nephritis                           |
|                        | **Anti-IFN-α/-γ**            | Sifalimunab: No results released                                           |
|                        | **Anti-IL-1**                | Anakinra: Improvements in SLE arthritis                                    |
|                        | **Anti-IL-6**                | Tocilizumab: Clinical and serologic improvements in SLE                     |
|                        | **Anti-IL-10**               | B-N10: Improvements in disease activity                                     |
| Other potential targets | **Anti–C5 monoclonal antibody** | Eculizumab: Improvements in SLE                                            |
|                        | **Soluble recombinant complement C3 inhibitor** | SCRI1 (TP10, BRL 55736): Improvements in disease activity                 |
|                        | **Chemokine (MCP)**          | Bindarit: Improvements in disease activity                                  |

**Rituximab**

Rituximab (RTX) is a chimeric monoclonal antibody that binds CD20, a protein expressed on B cells at all stages of development. Multiple open-label studies have reported the efficacy of RTX in patients with severe refractory SLE and catastrophic anti-phospholipid syndrome with maximal clinical benefit to be evident even after 18 months.[^39] Case series clearly suggest that RTX ameliorates hemolytic anemia, thrombocytopenia, arthritis, and probably central nervous system vasculitis associated with SLE.[^40]

Two initial randomized, double-blind, placebo-controlled trials namely EXPLORER and LUNAR[^41,42] to objectively assess the efficacy and safety of RTX in generalized lupus or nephritis-specific lupus were not successful where all patients were given high doses of corticosteroids and immune-suppressives as well. But EXPLORER study showed significant improvement in anti-dsDNA and complement levels. But a recent review evaluated the use of RTX in 188 SLE patients from 35 studies, reporting efficacy rates approaching 90 percent.[^43]

In a recently published RITUXILUP study by Lightstone et al., the efficacy of treating lupus nephritis without maintenance steroids was tried using two doses of 1 g

(BAFF)/B lymphocyte stimulator, tumor necrosis factor (TNF) alpha, INF-α, IFN-γ, interleukin (IL)-12, IL-6, IL-10, and MCP-1.[^38] Over the last few years, multiple studies have targeted these and other appropriate pathways in the therapy of SLE as given in Figure 1. Newer molecules have been developed targeting these pathways as given in Table 4.
doses (375 mg/m2 IV weekly) used in severe or refractory cases. To summarize, although RTX cannot be considered first-line therapy for mild-to-moderate SLE, it is of benefit in severe refractory disease.

**Belimumab**

The B-lymphocyte stimulator (BLyS) is important for the survival of B cells, and studies have shown overexpression of BLyS in SLE with higher BLyS levels correlating with SLE disease activity. Belimumab is a fully human monoclonal antibody that selectively targets and inhibits BLyS resulting in autoreactive B cell apoptosis.

In serologically active SLE patients, Belimumab led to a significantly better response over placebo and led to a significant reduction in B-cell counts, rise in complement levels, and reduction in immunoglobulin levels and anti-dsDNA levels. Belimumab was further evaluated in two large randomized, double-blind, placebo-controlled, multicenter phase 3 trials, BLISS-52 and BLISS-76 including 865 and 826 seropositive SLE patients, respectively. Belimumab was well tolerated, achieved significantly better results, delayed time to first SLE disease flare, and led to significant reduction in steroid doses than placebo.

It is the first and the only biologic agent approved for the treatment of refractory SLE. It is used in doses of 10 mg/kg IV q 2 Weeks x 3 doses, then q 4 Weeks thereafter.

**Other agents used**

**Epratuzumab**

Epratuzumab has been used to treat patients with SLE with neuropsychiatric and cardio-respiratory symptoms of SLE, which are resistant to conventional therapies. The dosage is 360 mg/m2, IV, every 2 weeks, for 4 doses.

**Atacicept**

Atacicept is a recombinant fusion protein, which inhibits B cell stimulation. It was tried in SLE patients, in which reductions up to 60% of mature and total B-cell populations was seen.

**Abatacept**

Abatacept has shown benefit in SLE patients with non-life-threatening manifestations and is found to be superior to placebo in reducing symptoms and improving quality of life and reducing flares. Animal data suggest a beneficial role of T-cell co-stimulation blockade (Abatacept) SLE models.

**TNF α inhibitors**

Two large randomized trials evaluated the efficacy and safety of TNF inhibitors (infliximab, etanercept) in SLE, but both were terminated prematurely and, therefore, they are not used for SLE. The use of these is commonly associated with the induction of lupus autoantibodies and anti-TNF-induced lupus (ATIL) which can have different levels of cutaneous, renal and neurological involvement. It can be prevented by concomitant immunosuppression and is treated by withdrawal of TNF inhibitors and steroids and/or immunosuppressive therapy (in severe cases).

**Tocilizumab (IL-6)**

Interleukin-6 (IL-6) is a key proinflammatory cytokine. Tocilizumab used in doses of 2-8 mg/kg twice weekly for 12 weeks led to reduction in inflammatory markers and auto-antibody levels in SLE.

**Abetimus**

It is an intravenously administered tetrameric oligonucleotide conjugate that safely reduces anti-dsDNA antibodies. Its use was associated with reductions in circulating anti-dsDNA antibodies. However, two pivotal trials in lupus nephritis failed to demonstrate statistically significant improvement.

**Eculizumab**

Furie *et al.* reported the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single administration of eculizumab (0.1, 0.75, 2, 4, and 8 mg/kg) in 24 patients with SLE. Eculizumab was well tolerated, achieved significantly better results, delayed time to first SLE disease flare, and led to significant reduction in steroid doses than placebo.

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**Haemoptic stem cell transplant (HSCT)**
In patients with severe SLE refractory to conventional immunosuppressive treatments, allogenic HSCT can achieve sustained clinical remissions (ranging from 50% to 70% disease-free survival at 5 years) associated with qualitative immunological changes.\[65\]

**Conclusion**
In recent years, advances in our understanding of the mechanisms of SLE have offered newer diagnostic modalities and better drug targets for treatment. Over the next years, we will test the efficacy of many new therapeutic agents. The coming years promise to be an exciting time for the development and trial of new pharmacological treatments and immunotherapies for patients with SLE as we benefit from improved understanding of disease pathogenesis and molecular mechanisms.

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**How to cite this article:** Shankar S, Behera V. Advances in management of systemic lupus erythematosus. J Mahatma Gandhi Inst Med Sci 2014;19:28-36.

**Source of Support:** Nil, **Conflict of Interest:** None declared.