Systemic Lupus Erythematosus: 
the rheumatologists’ perspective

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Summary

Systemic Lupus Erythematosus (SLE) is a disease characterized by a complex clinical and laboratory pattern; its clinical evolution is characterized by the overlapping of disease activity, potential organ damage and associated comorbidities. All these issues should be considered in the clinical and therapeutic management of patients with SLE. In the last few years, the disease prognosis has improved thanks to more advanced therapeutic protocols. However, several patients still have a disease activity which is not persistently controlled by therapy and which is characterized by frequent exacerbations, irreversible organ damage development, with a potential mortality higher than in the general population. The development of new drugs and the improved knowledge on the disease pathogenic mechanisms will help to improve the disease control and to reduce organ damage accumulation. Moreover, the detection of biomarkers that will help to prevent possible exacerbations could also allow to implement individualized therapies.  

KEY WORDS: Lupus Erythematosus; organ damage; therapy; prognosis.

Systemic Lupus Erythematosus (SLE) is one of the most difficult diseases of the internal medicine setting; it has been attributed several definitions, all sharing the evidence that the diagnosis in these patients is very hard to make. “Systemic autoimmune disease characterized by the involvement of multiple organs and a wide range of clinical manifestations which can change over time”, is the definition by the American College of Rheumatology, but in the Primer on the Rheumatic Diseases – the most classical educational project of the American Arthritis Foundation – it is defined as “Systemic autoimmune disease characterized by a wide range of clinical manifestations...”. The famous Californian rheumatologist Dubois, who authored the first huge volume on lupus, defined it as “A chronic polymorph disease with classical pattern ...”.

In the past, SLE was seen as a disease having a thousand different presentations and it was difficult to identify its specific pattern. SLE main clinical features include an extremely wide range of clinical manifestations – with varying degrees of severity – often alternating phases of remission and relapsing, with progressive chronic development of organ damage. This inevitably results into an impact on the patients quality of life; furthermore, the clinical outcome is frequently aggravated by the adverse events than can be caused by chronic systemic treatments and by accrual of comorbidities over time, of these treatment-being related as well.

Moreover, with regard to the definition of SLE as a disease with a chronic course, the authors agree that it can be characterized by periods of relapsing and remission which can even be spontaneous. The main clinical manifestations observed in 324 patients from the rheumatology unit of Pisa are reported in Table 1: this data shows that 72% of patients suffer from arthritis, in 31 cases deforming arthritis; hematological manifestations are also very common: firstly leukopenia followed by thrombocytopenia and haemolytic anemia. One of the most frequent organ involvement is lupus nephritis and grade IV diffuse proliferative nephritis is the most frequent histological type. In the same cohort, the impact of lupus-specific skin manifestations is also very common: firstly leukenopenia followed by thrombocytopenia and haemolytic anemia. One of the most frequent organ involvement is lupus nephritis and grade IV diffuse proliferative nephritis is the most frequent histological type. In the same cohort, the impact of lupus-specific skin manifestations is also impressive: acute skin rash was observed in about half of the cases, subacute lupus in 32 cases, discoid lupus in 23 cases. Also, serositis are very common in the form of pericarditis, pleuritis or, more rarely, peritonitis. Another unsolved and extremely serious problem is represented by the neuropsychiatric manifestations experienced by one quarter of the patients examined.  

These clinical associations were highlighted in the ACR (American College of Rheumatology) classification criteria in 1982 (1) which required – for classification purposes – the presence of at least four of the clinical manifestations listed in Figure 1.
More recently, the Systemic Lupus International Collaborating Clinics proposed a new set of clinical and immunological criteria for classifying SLE (Figure 2). In order to confirm a diagnosis, the presence of at least four criteria of those listed is deemed necessary (at least one clinical and one laboratory criteria) (2). This short clinical summary highlights the diagnostic difficulties that can be encountered by specialists in the clinical practice when they visit patients who present with a wide range of different and variable manifestations (3, 4).

Once the diagnosis is confirmed, the treatment main objective is to stabilize the disease activity in order to obtain remission of the inflammatory process – possibly without sequelae. The treatment should be modulated according to the clinical trend of the disease course: it is usually addressed to the induction of remission and then to maintaining the therapeutic response obtained. According to the available data, it is possible to identify three different patterns of progression in the disease history: the first one is characterized by clinical flares and remissions over time, the second one showing prolonged periods of clinical latency, and the third pattern when SLE is defined as “chronically active”.

According to the recent literature, the pattern characterized by clinical relapsing and remission can be seen in about one third of the patients, but it should also be kept in mind that less than ¼ of the patients obtains complete remission (absence of any clinical or serological sign), while in 40 to 52% of the cases – depending on the different studies – the disease has a typical chronic-active pattern (5, 6).

It should be highlighted that during the first year of the disease only 27.5% of the patients shows a clinical pattern that can be classified as quiescent (6).

The disease prognosis has considerably improved over the years (Figure 3). Physicians have certainly

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**Table 1 - Main clinical manifestations observed in the cohort of patients with SLE from the Rheumatology Unit of Pisa.**

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>232/324 (72%)</td>
</tr>
<tr>
<td>• Deforming arthritis</td>
<td>31</td>
</tr>
<tr>
<td>Haematological manifestations</td>
<td>226/324 (70%)</td>
</tr>
<tr>
<td>• Leukopenia</td>
<td>187</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>83</td>
</tr>
<tr>
<td>• Haemolytic anemia</td>
<td>71</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>185/324 (57%)</td>
</tr>
<tr>
<td>• Biopsies performed</td>
<td>157</td>
</tr>
<tr>
<td>• Class IV</td>
<td>121</td>
</tr>
<tr>
<td>• Class III</td>
<td>16</td>
</tr>
<tr>
<td>• Class II</td>
<td>13</td>
</tr>
<tr>
<td>• Class V</td>
<td>3</td>
</tr>
<tr>
<td>• Sclerosis</td>
<td>2</td>
</tr>
<tr>
<td>• Normal</td>
<td>2</td>
</tr>
<tr>
<td>“Lupus-specific” skin manifestations</td>
<td>182/324 (56%)</td>
</tr>
<tr>
<td>• Acute skin lupus (malar rash)</td>
<td>164</td>
</tr>
<tr>
<td>• Subacute lupus</td>
<td>32</td>
</tr>
<tr>
<td>• Discoid lupus</td>
<td>23</td>
</tr>
<tr>
<td>Serosites</td>
<td>125/324 (39%)</td>
</tr>
<tr>
<td>• Pericarditis</td>
<td>88</td>
</tr>
<tr>
<td>• Pleuritis</td>
<td>85</td>
</tr>
<tr>
<td>• Peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Neurological manifestations</td>
<td>75/324 (23%)</td>
</tr>
</tbody>
</table>

**ACR criteria (1982)**

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral aphthosis
5. Arthritis
6. Pleuritis/pericarditis
7. Renal involvement
8. Neurological involvement
9. Haematological alterations
10. Immunological alterations: LE cells, SJS false positive, anti-dsDNA, antiSm
11. Antinuclear antibodies

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**SLICC criteria**

**Clinical criteria**

- Acute cutaneous lupus, or subacute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers
- Non scarring alopecia
- Synovitis (2 or more joints)
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leukopenia/lymphopenia
- Thrombocytopenia

**Immunological criteria**

- ANA above laboratory reference range
- Anti-dsDNA above laboratory reference range, except ELSA (twice above lab reference range)
- Anti-Sm
- Anti-phospholipid
- Low complement
- Direct Coombs test in the absence of hemolytic anemia

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**Figure 1 - Clinical criteria for SLE classification according to the American College of Rheumatology (ACR) in 1982.**

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**Figure 2 - Clinical and immunological criteria for SLE classification according to Systemic Lupus International Collaborating Clinics (SLICC).**

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**Figure 3 - SLE and survival rate.**
learnt a lot on how to manage these patients, how to identify them and therefore how to treat them earlier, thanks to increasingly accurate diagnostic tools. However, this trend seems to have reached a plateau; over the last few years survival rate has improved, but it's stabilizing (7, 8).

The main causes of death in patients with SLE are cardiovascular events in 48.15% of cases, followed by infections in 29.63%; it is very interesting to observe that disease activity is considered to be a concomitant cause of death in association with other factors (organ involvement, infections) in 26% of the cases observed (6, 7). But what is the most unfavorable prognostic factor? All uncontrolled episodes of disease activity associated with possible drug treatment-related adverse events, cause a permanent damage which accumulates; this is also confirmed by the fact that survival is substantially very good in patients with a very low damage index. The more the damage index increases, the more survival seems to decrease: therefore damage accumulated over time considerably affects prognosis (8).

If we observe damage accumulation during the course of the disease, we can see that it is limited during the first year and then it progressively increases; indeed up to 50% of the patients observed during an average follow up of fifteen years shows significant permanent organ damage (8-10). Nowadays, the main predictors of damage are disease activity over time, the cumulative dose of corticosteroids, as well as the use of cyclophosphamide (10). With regard to the use of drugs, it is necessary to take into consideration the main adverse events which may occur in patients on chronic therapy who require repeated multiple drug treatments and high dosages. In patients with long-term disease, osteoporosis can be seen in 10.3% of cases vs 2.3% expected cases in the general population, and osteopenia in 23.9% vs 16.4% expected cases. In order to avoid this problem or at least to limit the damage, a supplementation of Vitamin D can be considered when initiating therapy, as well as dietary calcium intake and periodical bone density examination (11-15).

The association between cardiovascular complications and SLE is a very important research topic. It has been demonstrated that patients with SLE have a 50-fold increased risk of acute myocardial infarction (AMI) and that the mean age at AMI is 49 years as compared to 65-74 of the general population (11, 12). It is also important to highlight that 20-40% of patients with SLE have a subclinical cardiovascular disease. The need to receive immunosuppressive therapies for prolonged periods of time has highlighted the issue of the risk of infections in patients with SLE (Table 2) (16).

Data available seem to show a higher incidence of tuberculosis in patients with SLE, while HIV, HCV and HBV infections seem to be similar to those of the general population (16). Recommendations include the periodical screening for cytomegalovirus infections (16). Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 2 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients. Table 3 reports the main recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients.

Table 2 - Recommendations for infection screening in patients with SLE receiving pharmacological therapy.

<table>
<thead>
<tr>
<th>Recommendation #4 Infection risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># 4.1 Screening</strong></td>
</tr>
<tr>
<td>- We recommend that patients should be screened for:</td>
</tr>
<tr>
<td>- HIV based on patient's risk factors,</td>
</tr>
<tr>
<td>- HCV, HBV based on patient's risk factors, particularly before immunosuppressive (IS) drugs including high dose corticosteroids are started,</td>
</tr>
<tr>
<td>- Tuberculosis, according to local guidelines, especially before IS drugs including high dose corticosteroids are started,</td>
</tr>
<tr>
<td>- CMV testing should be considered during treatment in selected patients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence and Grade of recommendation</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b, C</td>
<td>98.8</td>
</tr>
</tbody>
</table>

Table 3 - Recommendations issued by the Centers for Disease Control and Prevention concerning indications on the vaccination of immunocompromised patients.

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Tetanus, diphtheria, pertussis, influenzae, pneumococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended if other risk factors are present</td>
<td>Hepatitis A and B, meningococcus</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>Measles, parotitis, rubella, chicken pox</td>
</tr>
</tbody>
</table>

Finally, it should be reminded that SLE is also associated with an increased incidence of haematological cancers (non-Hodgkin lymphoma) and uterine cervix cancer: 16% of the examined patients showed an altered cervicovaginal cytology; with regard to this, it is useful to remind that cyclophosphamide treatment increases the risk of altered cervicovaginal cytology (16).

References

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