Systemic lupus erythematosus

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Systemic lupus erythematosus is a remarkable and challenging disorder. Its diversity of clinical features is matched by the complexity of the factors (genetic, hormonal, and environmental) that cause it, and the array of autoantibodies with which it is associated. In this Seminar we reflect on changes in its classification criteria; consider aspects of its more serious clinical expression; and provide a brief review of its aetiopathogenesis, major complications, coping strategies, and conventional treatment. Increased understanding of the cells and molecules involved in the development of the diseases has encouraged the identification of new, better targeted biological approaches to its treatment. The precise role of these newer therapies remains to be established.

Introduction

Systemic lupus erythematosus is a challenging disease to assess and manage. The progress in our understanding of its aetiopathogenesis is notable. In this Seminar we provide an update on its clinical presentations and conventional management. We also review some of the many studies published in the past decade that used biological drugs, the development of which has been based on improved understanding of the causes of this disease. However, success in treatment of systemic lupus erythematosus with biological strategies is less impressive than that for rheumatoid arthritis. This difference is attributable to the complexity of the disorder and the likely diverse mechanisms that contribute to its clinical expression. This extra challenge makes the work of scientists, who seek to understand the disease better, and clinicians treating patients with lupus, more demanding.

Epidemiology

The incidence and prevalence of systemic lupus erythematosus seems to be increasing, probably because of both the identification of milder cases and improved survival. In 2007, a review outlined the geographical variability in disease incidence and prevalence. In the US population, the all-race incidence was 5·1 per 100,000 per year and the prevalence was 52·2 per 100,000, with comparative figures of 3·8 and 5·1 per 100,000 per year and the prevalence was 26·2 in the UK, and 2·9 and 28·4 in Japan, respectively.1 This difference is attributable to the complexity of the factors (genetic, hormonal, and environmental) that cause it, and the array of autoantibodies with which it is associated. In this Seminar we reflect on changes in its classification criteria; consider aspects of its more serious clinical expression; and provide a brief review of its aetiopathogenesis, major complications, coping strategies, and conventional treatment. Increased understanding of the cells and molecules involved in the development of the diseases has encouraged the identification of new, better targeted biological approaches to its treatment. The precise role of these newer therapies remains to be established.

Occurrence and mortality

The activity of disease and infections (28·9% each) were major causes of mortality during the first 5 years of follow-up. Thrombosis (26·1%) was the most common cause of death during the last 5 years of the study. The presence of antidouble-stranded DNA antibodies was a predictor of nephritis (relative risk 1·79) and haemolytic anaemia (2·49), and lupus anticoagulant predicted clinical antiphospholipid syndrome (1·2–1·53). The 10 year survival was 92%, which is significantly better than mortality rates reported earlier in the 20th century. The activity of disease and infections (28·9% each) were major causes of mortality during the first 5 years of follow-up. Thrombosis (26·1%) was the most common cause of death during the last 5 years of the study. The mortality risk has decreased substantially over past decades. In a cohort of 1241 patients with lupus from a clinic in Toronto, the standardised mortality ratio

Search strategy and selection criteria

We searched PubMed (January, 2009, to September, 2013) and Summon Search (January, 2009, to September, 2013) databases with the terms “systemic lupus erythematosus” and “lupus” in combination with the terms “epidemiology”, “classification”, “cardiovascular risk”, “lupus nephritis”, “CNS lupus”, “antiphospholipid syndrome”, “pregnancy”, “pathogenesis”, “presentation”, and “management”, with no language restrictions. We also searched the references of articles identified by this strategy and selected those that were relevant.
changed from 12·60 in the 1970s, to 3·46 in the past decade.\(^7\) Despite the improved mortality rate, patients with systemic lupus erythematosus have a higher mortality risk than that of the general population, particularly in patients with a younger age at disease onset.\(^7\) Furthermore, in developed countries with high gross domestic product, survival is much higher because of better access to health care, educational level, physician availability, and treatment compliance.\(^6\)

Clearly the outcome for systemic lupus erythematosus depends on more than just the development of new drugs. Furthermore, in some countries the funding for such drugs is not available. Some differences in outcome are evident in terms of ethnic origin. In the Lupus cohort at University College Hospital, London, UK, black patients with renal disease were far more likely to go into renal failure than were white patients;\(^7\) with the reasons almost certainly nothing to do with economics since health care is free at the point of entry in the UK’s National Health Service. In similar studies in the USA economic and genetic factors have been hard to disentangle.

**Revised classification criteria**

Since the publication of the last Seminar on systemic lupus erythematosus in *The Lancet* in 2007,\(^8\) a major development has been the publication of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria in 2012.\(^8\) This classification attempted to rationalise the clinical criteria and provided a modest expansion in recognised laboratory abnormalities (panel 1). Biopsy-proven nephritis compatible with systemic lupus erythematosus in the presence of antinuclear or antidouble-stranded DNA antibodies in the absence of other lupus features is regarded as sufficient for a patient to be diagnosed as having lupus. The symptoms and laboratory abnormalities are cumulative and need not to be present concurrently.

**Pathogenesis**

Systemic lupus erythematosus is a multifactorial disease with evidence of genetic susceptibility, environmental effects, and disturbances in both innate and adaptive immune function by disturbances in apoptotic cell clearance, cytokines, B-cell immunity, and T-cell signalling. Although a detailed review of the pathogenesis of lupus has been published,\(^9\) we briefly summarise some noteworthy developments.

Deficiencies in components of the complement cascade are well known to predispose to the development of systemic lupus erythematosus. However, more than 28 other disease susceptibility loci have now been confirmed.\(^9\) Some of the strongest associated risk loci identified through genome-wide association studies are ITGAM, FcγR, PRDM1-ATG5, and TNFAIP3. Whether these loci will help to identify additional inflammatory pathways implicated in the disorder that will translate into novel therapeutic targets is unknown.

Lupus is strongly associated with defects in apoptotic clearance.\(^9\) The initiating events are likely to vary, but the consequent excessive apoptotic debris has an important pathogenic effect. Early apoptotic cells express so-called eat-me signals—ie, cell-surface proteins such as phosphatidylinerine that prompt circulating immune cells to engulf these cells. They also express so-called find-me signals to attract macrophages and dendritic cells. Failure of phagocytes to remove apoptotic material efficiently

### Panel 1: Clinical and immunological criteria used in the Systemic Lupus International Collaborating Clinics (SLICC) classification system*

**Clinical criteria**

1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of systemic lupus erythematosus, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus (psoriaform or annular polycyclic lesions, or both)
2. Chronic cutaneous lupus, including classic discoid rash (localised and generalised), hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, and discoid lupus/lichen planus overlap
3. Oral ulcers or nasal ulcers
4. Non-scarring alopecia
5. Synovitis involving two or more joints and at least 30 min of morning stiffness
6. Serositis
7. Renal (urine protein-to-creatinine ratio [or 24 h urine protein]) representing 500 mg protein per 24 h or red blood cell casts
8. Neurological: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathy, acute confusional state
9. Haemolytic anaemia
10. Leukopenia (<4000 cells per μL at least once) or lymphopenia (<1000 cells per μL at least once)
11. Thrombocytopenia (<100 000 cells per μL) at least once

**Immunological criteria**

1. Antinuclear antibody concentration greater than laboratory reference range
2. Antidouble-stranded DNA antibody concentration greater than laboratory reference range (or two-fold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium-titre or high-titre antiphospholipid antibody concentration (IgA, IgG, or IgM), or positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement C3, low C4, low CH50
6. Direct Coombs’ test in the absence of haemolytic anaemia

*See full description of the criteria in reference 6.*
leads to fragments of nuclear particles being captured by antigen presenting cells, and through interactions with T and B cells ultimately to the development of the antinuclear antibodies that are typical of the disease.

There are bridging molecules between apoptotic cells and phagocytes. A high concentration of one such molecule, MFG-E8, has been reported in some patients with childhood-onset and adult systemic lupus erythematosus. Excess MGF-E8 can have an inverse effect on the engulfment of apoptotic cells.

Studies have shown intense polyclonal B-cell activation in patients with systemic lupus erythematosus. There is a population shift towards more immature B cells that is independent of disease activity. Disturbances in memory B cells in peripheral blood in patients with lupus include increased CD27+/IgD– post-switched memory cells that are less susceptible to immunosuppression, and CD27-/IgD– memory B cells are increased and associated with disease activity and renal lupus. A population of regulatory CD19+/CD24 (high)/CD38 (high) B cells secreting interleukin 10 that lack functionality has been reported in patients with lupus.

T cells regulate B-cell responses and infiltrate target tissues causing damage. T cells in patients with lupus have properties of activated/effector cells and are somewhat anergic in state. Studies have shown defects in early and intermediate signalling, adhesion and co-stimulation, gene transcription, and alternative splicing implicating T-cell dysfunction in disease pathogenesis.

B-lymphocyte stimulator (BLys), interleukin 6, interleukin 17, interleukin 18, type I interferons, and tumour necrosis factor α (TNFα) are cytokines that are involved in the inflammatory process and tissue injury in patients with lupus. The growing knowledge of these cytokines provides an opportunity for their clinical applications.

Environmental and hormonal factors
Ultraviolet light is the most well described environmental trigger of systemic lupus erythematosus. Both ultraviolet A2 and ultraviolet B exposure, including through cosmetic sun tanning, can exacerbate skin disease in patients with the disorder. However, the consequent avoidance of sunlight can lead to vitamin D deficiency, which is inversely related to disease activity. Thus periodic assessment and replacement is needed for patients deficient of vitamin D.

Pathologically, the effect of ultraviolet B on apoptosis induction seems to be dose dependent, with intermediate-dose and high-dose exposure associated with autoantigen release and cytokine production. Other organic and inorganic compounds such as silica dust, organic solvents, and petroleum might play a part in development of systemic lupus erythematosus. Panel 2 outlines triggering factors in this disease.

A recent addition to the list of iatrogenic causes (notably hydralazine and D penicillamine) of lupus or a lupus-like illness has been the TNFα inhibitors. There are differences, however, between classic drug-induced and anti-TNF-induced lupus. In particular, antidouble-stranded DNA antibodies and hypocomplementaemia are more common in anti-TNF-induced lupus. Despite the common finding of positive antinuclear antibodies in patients given TNF inhibitors, the rarity of anti-TNF-induced lupus is exemplified by data from the British Society for Rheumatology’s Biologics Registry. Of 11394 patients given anti-TNFα, only 40 developed lupus-like features, with skin rash being the most common symptom.

The incidence of systemic lupus erythematosus is well known to increase after puberty and decrease after menopause, and the severity of disease varies with pregnancy and menstrual cycle. In a cohort of 238308 women followed up prospectively between 1976 and 2003, factors such as early menarche, oral contraceptive use, early menopause, surgical menopause, and postmenopausal use of hormones were associated with increased risk of systemic lupus erythematosus. Use of combined hormone replacement therapy in 351 menopausal women was associated with a small risk of increasing mild-to-moderate flare-ups.

Cardiovascular risk
The recognition that atherosclerosis is closely linked with the immune system is reflected in the well described association of many chronic inflammatory disorders with a predilection for enhanced atherogenesis. Systemic lupus erythematosus is no exception. Prevalence varies according to the study population, with estimates ranging from 6% to 10%. Most striking, however, is that in women aged 35–44 years with lupus, the risk of myocardial infarction is increased 50 times, compared with an age-matched and sex-matched general population. Vascular events, not surprisingly, contribute substantially to the increased mortality in patients with systemic lupus erythematosus. In one study of 208 patients with this disorder followed up over 12 years, 48 died at a mean age of 62 years. Cardiovascular disease
was the leading cause of mortality in this cohort (48%). Many studies have shown that subclinical atherosclerosis is present in a large proportion of patients with systemic lupus erythematosus, in which surrogate measures such as carotid intima media thickness were used, and with high rates of endothelial dysfunction assessed by flow-mediated vasodilation.28

The mechanisms underlying this enhanced risk are not fully understood. Traditional vascular risk factors have a role, but do not fully explain the excess event rate. Many theories have been suggested, largely concentrating on aberrant immune pathways, some with conflicting reports. Some of these theories include excess monocyte activation, the presence of antiphospholipid antibodies, dysregulation of the complement system, oxidative stress (homocysteine, paraoxonase), and variable antibodies (to endothelial cells, antiatherogenic HDL, antilipoprotein lipase, oxidised LDL, C-reactive protein, etc). Many cytokines have also been suggested as theoretical mediators of atherogenesis (TNFα, interferon γ, interleukin 17, adiponectin). Interferon α is an attractive candidate because of its association with systemic lupus erythematosus and its role as a mediator of aberrant vascular repair. The proposed mechanism is repression of the proangiogenic factor interleukin 1β and vascular endothelial growth factor, and upregulation of the antiangiogenic interleukin 1 receptor antagonist.29 Increased serum interferon type 1 activity is associated with decreased endothelial function and severity of coronary calcification in patients with lupus.30

Although differences in the traditional cardiovascular risk factors alone do not account for the increased risk in patients with systemic lupus erythematosus,2 assessing and addressing these modifiable factors is clearly a necessity. Thus, encouraging patients to stop smoking, and optimising their blood pressure, lipid profile, and control of disease activity are essential to decrease cardiovascular morbidity. With specific reference to therapeutic agents used for control of disease activity in systemic lupus erythematosus, some theoretical evidence supports a role for hydroxychloroquine in view of its antithrombotic and lipid-modifying properties.21,31 Additionally, mycophenolate mofetil might confer protection from vascular disease, although data are conflicting.14 Therefore, until more disease-specific evidence is available the best strategy to minimise risk of cardiovascular disease is to treat active disease while monitoring for traditional vascular risk factors.

Lupus nephritis

Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) groups have published revised guidelines for the assessment and management of lupus nephritis. The previous ACR guidelines, published in 1999, recommended use of glucocorticosteroids and cyclophosphamide as induction therapy for proliferative lupus nephritis. Mycophenolate mofetil was not widely available at that time. Since then several trials have shown non-inferiority of this drug to cyclophosphamide for the induction treatment of lupus nephritis. Moreover, it might be a superior therapeutic approach in particular populations, such as African-Americans. Thus both the ACR and EULAR groups now advocate the use of either cyclophosphamide or mycophenolate mofetil as induction strategies for lupus nephritis.

The Euro-lupus regimen (six pulses of intravenous cyclophosphamide every 2 weeks at a dose of 500 mg)32 provides the opportunity to treat patients with lupus nephritis effectively with lower doses of cyclophosphamide and a reduced infection risk. Many centres now use it in preference to the older regimen recommended by the US National Institutes of Health (monthly intravenous cyclophosphamide 750 mg/m² body surface area for 6 months, followed by intravenous cyclophosphamide every 3 months for 2 years).

Other recommendations include the use of the renin-angiotensin-aldosterone system (RAAS) blockers to manage proteinuria and hypertension, and the use of hydroxychloroquine.33 Patients receiving hydroxychloroquine had higher rates of renal response, fewer relapses, and reduced accrual of renal damage than did those who did not receive hydroxychloroquine. Control of cardiovascular risk factors should be managed in a similar manner to that for patients without lupus.

Azathioprine can be considered for milder cases of disease on the basis of results of the biopsy sample. If lupus nephritis induction strategies are not effective, switching to another agent or to rituximab is suggested.34 Although either mycophenolate mofetil or azathioprine can be used to maintain remission, there is some suggestion that mycophenolate mofetil might be more efficacious.35

CNS lupus

The pathogenesis of neuropsychiatric lupus is multifactorial, probably varies between individuals, and involves autoantibodies, immune complexes, and cytokines.36,37 Twenty autoantibodies detected in the serum or cerebrospinal fluid of patients with neuropsychiatric lupus have been reported.38 They were categorised into brain-specific (n=11) and systemic (nine) autoantibodies. Brain-specific autoantibodies included those binding neuronal, brain reactive (BRAA), N-methyl-D-aspartate receptor (NMDA), ganglioside, microtubule-associated protein 2 (MAP-2), neurofilament, and glial fibrillary acidic proteins. The most common autoantibodies in patients with neuropsychiatric lupus, however, were anticardiolipin antibodies. These antibodies correlated with cognitive impairment, depression, psychosis, chorea, seizures, and migraine. To distinguish features due to CNS lupus from those of antiphospholipid syndrome is a challenge.
Antiphospholipid syndrome

Antiphospholipid syndrome can be primary or secondary. It is characterised by recurrent venous or arterial thrombosis or pregnancy morbidity, and persistent presence of antiphospholipid antibodies. Although 30–40% of patients with lupus have antiphospholipid antibodies, the antiphospholipid syndrome complicates only 10–15% of cases of systemic lupus erythematosus. About 40 antiphospholipid antibodies have been described so far, but only three are used for the confirmation of diagnosis.46 Triple positivity for lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein 1 antibodies (at least one must be positive for the diagnosis of antiphospholipid syndrome on two or more occasions 12 weeks apart)42 has a strong association with the clinical symptoms of this syndrome. Recent interest has centred on the thrombogenic mechanisms of antiphospholipid antibodies, with particular interest in β2-glycoprotein.

Antiphospholipid syndrome has a wide range of clinical features, depending on the site of thrombosis. Growing evidence suggests that atherosclerosis might occur early in these patients. In a cohort of 49 patients with primary antiphospholipid syndrome (mean age 37 years), investigators detected premature subclinical atherosclerosis, measured by the carotid intima media thickness.41

The therapeutic approach to antiphospholipid syndrome is based on modification of the general risk factors for thrombosis and use of antplatelet and anticoagulant agents, notably heparin or warfarin. However, a trial comparing rivaroxaban (an inhibitor of factor Xa) and warfarin in patients with thrombotic antiphospholipid syndrome is in progress.46 Rivaroxaban has few reported drug interactions, no food or alcohol interactions, and does not need routine monitoring because of a predictable dose-response correlation. There is also some evidence for the usefulness of statins, hydroxychloroquine, and rituximab for the treatment of patients with antiphospholipid syndrome.

Statins are a very attractive addition to the drug regimen used for treatment of this syndrome. They modulate the proinflammatory mechanisms of small GTPases and prenylated proteins without complete inhibition of these crucial signalling pathways.6 Studies have shown the beneficial effects of statins in patients with antiphospholipid syndrome.46

The antithrombotic effects of hydroxychloroquine are presumed to be related to the inhibition of platelet aggregation and arachidonic acid release from stimulated platelets and additional effects on suppressing disease activity and modifying lipid profile.6 In a study of 90 patients with systemic lupus erythematosus who had antiphospholipid antibodies, the use of hydroxychloroquine was associated with significantly lower odds of having persistent positivity to lupus anticoagulant or anticardiolipin antibodies (>40 U), or both.39

Finally, a summary of 21 case reports on the use of rituximab in patients with antiphospholipid syndrome showed a beneficial effect in 19 cases.50 The concentrations of antiphospholipid antibodies were significantly decreased in ten of 12 cases. In a further cohort of 32 patients with systemic lupus erythematosus who were given rituximab, interesting results were noted in relation to anticardiolipin antibodies after B-cell depletion. Seven patients were positive for IgG anticardiolipin antibodies before treatment, six of whom achieved undetectable concentrations 6–9 months after B-cell depletion therapy.51

Pregnancy

Previously, women with lupus, especially lupus nephritis, might have been advised against contemplating pregnancy. Lupus does not affect fertility, but contraception and pregnancy planning have great importance in the routine care of patients with lupus. Many pregnant women with active lupus will develop complications such as preterm birth and pre-eclampsia. A third of lupus pregnancies will result in a caesarean section.52 A major factor linked to these complications is increased lupus activity at the time of conception and the presence of damage associated with systemic lupus erythematosus before conception.

Thus the goal for the timing of pregnancy is when there is minimum disease activity. Pre-pregnancy counselling includes information about the risk of complications, and planning antenatal care. Patients should ideally be followed up in high-risk obstetrics clinics, with multidisciplinary input to optimise maternal and fetal outcomes. Continuation of hydroxychloroquine and low-dose steroids seems to be safe in pregnancy and might prevent disease flares. Azathioprine can also be considered in patients with active systemic lupus erythematosus during pregnancy. Patients with secondary antiphospholipid syndrome should additionally receive anticoagulation.51

Patients with lupus nephritis are at particularly increased risk during pregnancy. A flare of this disease is most likely if there is active disease at conception. Class III and IV lupus nephritis is more likely to be associated with hypertension and pre-eclampsia than is class II and V disease.54 In patients with established renal disease, particularly with a creatinine concentration before pregnancy of more than 200 mmol/L, the physiological adaptations, such as increased renal blood flow and glomerular filtration rate, that occur during pregnancy are absent. This factor puts women at increased risk of renal impairment as a result of pregnancy. Because hypertension is a risk factor for fetal death in patients with lupus nephritis, control of blood pressure is important. The safe levels of blood pressure, however, are not established yet.

Women who possess antibodies to Ro (SSA) need additional monitoring. These antibodies can cross the placenta at about 12 weeks of gestational age. They can cause neonatal lupus syndrome, which includes cardiac...
and not the pregnancy.

proteinuria, are genuinely attributable to active lupus

ensure that abnormalities being recorded, such as

Clinics SLICC-2000. It is crucial with any index used to

such as the Systemic Lupus International Collaborating

in mothers who had difficulties in previous pregnancies

the probability of delivery of a second affected child is higher

in those who did not.55

regulation of cell-cycle initiation and differentiation of

expressed by pre-B and mature B cells. It has a role in the

sitional, activated mature B cells and finally into memory

in bone marrow. They mature into immature, tran-

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treatment of systemic lupus erythematosus, and panel 3

The table summarises the general approach to the

New treatments

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treatment of systemic lupus erythematosus, and panel 3

the drugs commonly used. We focus on new develop-
ments in lupus treatment.

Increasingly, patients with lupus who do not respond to
conventional immunosuppressive drugs are con-
considered for targeted biological therapies aimed at

cytokines, B and T lymphocytes, and B-cell activating
factors. Blockade of B lymphocytes is of particular
interest since lupus autoantibodies play an important
part in the pathophysiology of the disease. B cells develop
from haemopoietic stem cells into pro-B and pre-B cells
in bone marrow. They mature into immature, transi-
tional, activated mature B cells and finally into memory
and plasma cells in the periphery.

CD20 is a B-lymphocyte-specific antigen that is
expressed by pre-B and mature B cells. It has a role in the
regulation of cell-cycle initiation and differentiation of
the B-cell lineage. Rituximab is a chimeric monoclonal
IgG1 antibody to CD20 that causes B-cell depletion
lasting from 6 to 12 months and is mediated through
complement-dependent cytotoxicity, antibody-dependent
cellular toxicity, and apoptosis induction.67 Licensed for
the treatment of non-Hodgkin lymphoma, rheumatoid
arthritis, and vasculitis, there are several case and registry
reports of the use of rituximab in patients with systemic
lupus erythematosus with disease refractory to standard
treatments. However, two major clinical trials have not
met their endpoints;68,69

The EXPLORER trial68 assessed rituximab in
257 patients with moderate and severe systemic lupus
erythematosus. Patients were receiving methotrexate,
azathioprine, or mycophenolate mofetil, and 57% were
steroid dependent. The primary endpoint was achieving
and maintaining clinical response (BILAG C scores or
better in all eight organ system scores at week 24 and
maintaining it without moderate or severe flare-up to
week 52). Although the primary and secondary endpoints
were not achieved, beneficial effects were noted in
African-American and Hispanic patients.68

The LUNAR trial,69 a randomised, double-blind, placebo-
controlled trial, was undertaken in 144 patients with
class III or IV lupus nephritis treated concomitantly with
mycophenolate mofetil and corticosteroids. The primary
endpoint (rituximab superiority) was not achieved.10 The
reasons why the EXPLORER and LUNAR studies did not
reach their endpoints are conjectural but the large
amounts of concomitant steroids and immunosuppressive
drugs very probably played a part.

Generally, rituximab has been used when conventional
drugs have proven ineffective. However, Pepper and
colleagues9 proposed use of this drug at the time of
diagnosis of lupus nephritis, with the aim to avoid oral
steroids. A further small study71 used controls (3:1) who
were treated conventionally. The patients were given
azathioprine (Pepper and colleagues used mycophenolate

<table>
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<th>Typical manifestations</th>
<th>Mild activityflare</th>
<th>Moderate activityflare</th>
<th>Severe activityflare (non-renal)</th>
<th>Severe activityflare (renal)</th>
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<tr>
<td>Malar rash, arthritis, fatigue</td>
<td>Plaquenil 400 mg per day, NSAIDs, +/- analgesics</td>
<td>Prednisone 20–30 mg per day, could also add azathioprine 2–3 mg/kg per day, or methotrexate (about 15 mg/week), or mycophenolate mofetil (2–3 g per day)</td>
<td>Prednisone 30–50 mg per day (or methylprednisolone three doses of 500–750 mg intravenously) and mycophenolate mofetil 2–3 g per day or B-cell depletion. Cyclophosphamide orally or intravenously</td>
<td>Prednisone 30–50 mg per day, and Euro-Lupus IV cyclophosphamide protocol preferred to NIH protocol (see text) or mycophenolate mofetil 2–3 g per day or B-cell depletion</td>
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<td>Arthritis, pleuritis, pericarditis, crops of mouth ulcers, rash up to two-ninths body surface area, early renal involvement</td>
<td>Plaquenil 200 mg per day</td>
<td>Prednisone about 5 mg per day and initially azathioprine 50 mg per day; or methotrexate 10 mg per week; or mycophenolate mofetil 750 mg per day. Aim to stop immunosuppression eventually</td>
<td>Prednisone 5–7.5 mg per day and mycophenolate mofetil about 1 g per day or azathioprine 50–100 mg per day</td>
<td>Prednisone 7–5 mg per day or mycophenolate mofetil 1 g per day or azathioprine 50–100 mg per day</td>
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Table: Treatment strategies for systemic lupus erythematosus
Panel 3: Drugs used for treatment of systemic lupus erythematosus

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<th>Steroids</th>
<th>Methotrexate</th>
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<td>Potent immunosuppressive drugs</td>
<td>A folate antimetabolite that inhibits DNA synthesis.</td>
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<td>Induce anti-inflammatory</td>
<td>Binds to dihydrofolate reductase, resulting in decreased purine synthesis and cell proliferation.</td>
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<td>cytokines (interleukin 10,</td>
<td>Used for non-organ threatening disease manifestations such as skin and joint disease.</td>
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<td>interleukin 1Ra, and annexin-1)</td>
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<td>adhesion molecules and</td>
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<td>and tumour necrosis factor)</td>
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<td>and inhibit cyclo-oxygenase 2</td>
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<td>and inductive nitric oxide</td>
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<td>synthase.25 Used for all</td>
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<td>Non-steroidal anti-inflammatory</td>
<td>Ciclosporin</td>
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<td>drugs</td>
<td>Forms complex with cyclophosph in that disrupts the activation of calcineurin (complex of phosphatases).</td>
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<td>Analgesic, antpyretic, and</td>
<td>Inhibits production of interleukin 2 and arrests T-cell cycle between G0 and G1.44 Used for moderate to severe systemic lupus erythematosus and as a steroid-sparing drug.</td>
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<td>anti-inflammatory properties.</td>
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<td>Inhibit cyclo-oxygenase, types</td>
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<td>1 and 2. Used for fever,</td>
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<td>serositis, and arthritis.</td>
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<td>Hydroxychloroquine</td>
<td>Mycophenolate mofetil</td>
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<td>Immunomodulative properties</td>
<td>Mycophenolate (mycophenolic acid as active metabolite) inhibits monophosphate dehydrogenase and blocks synthesis of guanosine nucleotides and proliferation of T and B cells. Used for induction and maintenance therapy in lupus nephritis60 and in moderate to severe systemic lupus erythematosus.</td>
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<td>without immunosuppression.</td>
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<td>Increases lysosomal pH and</td>
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<td>receptor 9.18 Used for arthritis, skin rashes, and fatigue. Might have a useful role in nephritis, have antithrombotic properties, and reduce cholesterol concentrations.</td>
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<td>Cyclophosphamide</td>
<td>Tacrolimus</td>
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<td>Forms active alkylating</td>
<td>Calcineurin inhibitor effective in treatment of lupus nephritis63 and in cutaneous lupus.64</td>
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<td>metabolites (4-hydroxycyclophosphamide, phosphoramidum mustard, and acrolein). Prevents division of the cells by cross-linking DNA and suppressing DNA synthesis.</td>
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<td>Euro-lupus protocol recommends six pulses of intravenous cyclophosphamide at a dose of 500 mg every 2 weeks. Used for lupus nephritis36 and severe systemic lupus erythematosus.</td>
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<tr>
<td>Azathioprine</td>
<td>Leflunomide</td>
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<tr>
<td>Purine analogue that</td>
<td>Inhibits dihydro-oxorotate dehydrogenase necessary for pyrimidine and cellular protein kinases synthesis. Has immunosuppressive and antiviral effects.52</td>
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<tr>
<td>suppresses DNA synthesis by</td>
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<td>inhibiting synthesis of</td>
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<td>xanthyllic and adenyllic acids.</td>
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<td>36 Used for systemic features</td>
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<td>of lupus and maintenance</td>
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<td>therapy of lupus nephritis,</td>
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<td>class III and IV. An option as</td>
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<td>an induction therapy for</td>
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<td>selected patients with lupus</td>
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<td>nephritis who are very</td>
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<td>concerned about the risk</td>
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<td>of infertility associated with</td>
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<tr>
<td>cyclophosphamide,46 and helps</td>
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<td>to reduce the steroid</td>
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<td>requirement.</td>
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<td>Intravenous immunoglobulin</td>
<td>Biologics</td>
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<td>Consists of natural polyclonal</td>
<td>See panel 4.</td>
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<td>antibodies, mainly IgG fraction,</td>
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<td>pooled from the sera of</td>
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<tr>
<td>thousands of donors. Off-label use in catastrophic antiphospholipid syndrome.66 An option in patients with active disease but there are contraindications and limitations for use of immunosuppressive drugs, such as pregnancy or concomitant infections.</td>
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mofetil after rituximab (1 g given twice intravenously, 2 weeks apart) and, again, the aim was to minimise steroid prescription. The mean reduction of global BILAG score for patients with B-cell depletion was 12-0 points compared with 13-2 points in the conventionally treated patients (no significant difference). The mean cumulative prednisolone doses at 6 months were 1287-3 mg for patients with B-cell depletion versus 2834-6 mg in the control group.75

Condon and colleagues75 have reported the effect of rituximab as a steroid-sparing agent in 50 patients with lupus nephritis followed up for 2 years. Patients were given two doses of 1 g rituximab and methylprednisolone (both intravenously) at diagnosis followed by mycophenolate mofetil. This trial has shown encouraging results. With this regimen only two of 50 patients needed regular oral steroids at follow-up, and histological improvement was noted in nine of 13 repeat biopsies for persisting proteinuria.72 It is noteworthy that despite results from the EXPLORER and LUNAR trials, both ACR and EULAR guidelines suggest consideration of rituximab for patients with active lupus nephritis refractory to conventional therapies.

BLyS (or B-cell activating factor, BAFF) is a cytokine of the TNF family. It binds three receptors on the surface of the B lymphocyte: BlyS receptor 3 (BR3), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI), and B-cell maturation antigen (BCMA). Suppression of the binding of BLyS to BR3 causes apoptosis and inhibition of the maturation of B cells.73 Belimumab is a monoclonal human antibody that inactivates BLYS. It is approved in Canada and the USA, and is the first biological medication approved for the
treatment of patients with antibody-positive systemic lupus erythematosus who have active disease despite treatment with standard drugs.82

Two trials have supported the efficacy of belimumab in this setting.79,80 Both BLISS-52 and BLISS-76 met their primary endpoints with a belimumab dose of 10 mg/kg. In BLISS-52, 1 mg/kg was also effective. Patients had mainly skin and joint manifestations, but other occasional features such as pleurisy were present; however, patients with active renal disease or CNS involvement were excluded. The populations studied in the two trials differed: BLISS-52 recruited patients from Latin America, the Asia-Pacific area, and eastern Europe, whereas BLISS-76 recruited patients from North and Central America and Europe. Many patients were taking steroids (67–71% of patients took prednisone >7.5 mg in BLISS-52, and 44–48% in BLISS-76) and some also took other immunosuppressive drugs. The success of belimumab encourages other studies of molecules that block B-cell activating factors.

Atacicept is another agent that blocks the interaction between BLyS and APRIL (a proliferation-inducing ligand) and their receptors. APRIL has a function similar to BLyS.77 Atacicept is a recombinant receptor-Ig fusion protein that binds to BLyS and APRIL. It suppresses the differentiation and survival of antibody-producing B cells. Atacicept with mycophenolate mofetil was used in a trial of lupus nephritis that was stopped after the enrolment of six patients because of serious infections. Detailed analysis of these infections proved them to be mainly due to hypogammaglobulinemia induced by mycophenolate mofetil before atacicept had been given. The efficacy of atacicept was not assessed.78 The preliminary results of a major trial in non-renal lupus have indicated that atacicept might be effective at prevention of disease flare.79 The full results are awaited.

CD22 is a B-lymphocyte-specific transmembrane sigalicycoprotein. It is present in highest concentration on the surface of mature IgM+/IgD+ B cells and is absent on memory and plasma cells.80 CD22 functions through the B-cell receptor (BCR) complex by phosphorylation of three tyrosine-based inhibitory motifs on its intracellular part. Phosphorylation initiates the recruitment of the tyrosine phosphatase 1 molecules that inhibit BCR signalling. Epratuzumab is a humanised anti-CD22 IgG1 monoclonal antibody. Treatment with epratuzumab causes a decrease in the peripheral B lymphocyte count in patients with lupus. An initial open-label clinical trial of epratuzumab in 14 patients with moderately active systemic lupus erythematosus, which was undertaken in 2008, showed that epratuzumab was well tolerated and improved BILAG scores by more than 50% in 77% of patients at 6 weeks, and in all patients at some point during the study period.81 A phase IIb study of epratuzumab in 227 patients with moderate to severe lupus showed that patients had a symptom reduction or absence of active disease within specific body systems, especially cardiorespiratory or neuropsychiatric systems.82

Panel 4: Biological treatments available or potentially available for the treatment of systemic lupus erythematosus

<table>
<thead>
<tr>
<th><strong>Targeting B cells</strong></th>
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<tr>
<td>B-cell depleting therapy: rituximab</td>
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<td>B-cell modulating therapy: epratuzumab</td>
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<td>Inhibition of B-cell survival: belimumab, atacicept</td>
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<td>Other potential B-cell (plasma cell) targeting strategies: bortezomib</td>
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<td><strong>Targeting T cells</strong></td>
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<tr>
<td>Inhibition of T-cell function: abatacept, ruplizumab, toralizumab, lupuzor</td>
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<td><strong>Interleukin 6</strong></td>
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<td>• Tocilizumab</td>
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<td><strong>Tumour necrosis factor α inhibitors</strong></td>
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<tr>
<td>• Infliximab</td>
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<td>• Etanercept</td>
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<td><strong>Type I interferon inhibitors</strong></td>
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<tr>
<td>• Sifalimumab</td>
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<td>• Rontalizumab</td>
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<td><strong>Complement inhibitors</strong></td>
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<td>• Eculizumab</td>
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T cells have also been suggested as a therapeutic target in systemic lupus erythematosus. Abatacept is a biological drug that blocks T-cell costimulation. It is a fusion protein consisting of the T-lymphocyte-associated antigen-4 (CTLA-4) and modified Fc portion of human immunoglobulin.82 To be activated T lymphocytes require two signals: the antigen-specific signal 1 and costimulatory signal 2. CTLA-4 plays a part in the inhibition of costimulation; through its engagement with CD80/86, it causes inhibition of T-cell activation. In a double-blind, placebo-controlled trial of abatacept in patients with non-life-threatening lupus,118 patients were studied. The primary endpoint was the proportion of new flares after tapering of the steroid dose. The study did not meet the primary endpoint, but treatment differences were evident in patients with polyarthritic symptoms in post-hoc analyses.19–4% of patients in the study were negative for antinuclear and double-stranded DNA antibodies, which is substantially higher than in lupus cohorts in general.

Sifalimumab, a human anti-interferon α monoclonal antibody, binds and neutralises most interferon α subtypes. It prevents signalling through the type 1 interferon receptor. Two randomised, double-blind studies83,84 showed its safety, and results support the continued clinical development of strategies targeting interferon α for treatment of systemic lupus erythematosus. Other anti-interferon α molecules that have been going through testing in phase 2 studies are rontalizumab, AGS-009, MEDI-546, and interferon-α kinoid.85 Panel 4 summarises biological agents already available or potentially available for use for the treatment of systemic lupus erythematosus.
Coping with the disease and quality of life

Non-pharmacological management of systemic lupus erythematosus is also important. The psychological effects of lupus include depression, fatigue, psychological distress, and difficulties with emotion-oriented coping. A study of 120 patients with this disorder showed that treatment of depression, and consideration of stress and insomnia, reduced fatigue. Of 154 Australian and UK patients with lupus, 26% were clinically depressed. Depression and insufficient suitable coping mechanisms and support impair the ability to manage chronic disease effectively. Some studies indicate dissatisfaction with social support, notably poor understanding and unsatisfactory contact with the doctor or little information about the disorder. Ideally, patients with lupus should be assessed regularly for depression, and medical intervention and referral to psychology services should be available. Connecting the patient with support groups or societies available locally can relieve the frustration of searching unreliable internet sources.

A supervised cardiovascular training programme in patients with lupus substantially improves exercise tolerance, aerobic capacity, depression, and quality of life. A study of 60 patients who participated in a training protocol on a treadmill showed that the training group had a significant improvement in their aerobic capacity, as measured by the anaerobic threshold, and improvements in depression and quality-of-life scales. Supervised physical exercise also improves endothelial function and aerobic capacity without worsening of the disease activity in patients with systemic lupus erythematosus.

Conclusion

Understanding of the pathogenesis of lupus is clearly growing. Encouragingly, this knowledge is being applied in clinical practice with improvements in classification, a better appreciation of lupus features and complications, and the development of new drugs. There is better understanding of the importance of other aspects of lupus management such as quality of life, mental health, prevention of complications such as atherosclerosis, and pregnancy morbidity, and they play an important part in day-to-day practice. Despite the complexity and diversity of the disease there is hope for these patients. New promising agents targeting its different mechanisms are already used or in development.

Contributors

LL cowrote the first draft of this Seminar with GM, did much of the original literature search, and approved the responses to reviewers written by GM and DI. GM cowrote the first draft of this Seminar with LL, and modified some of the panels and table. DI set out the original plan for the Seminar, had a major contribution to redrafting the original version, and took responsibility for answering the reviewers’ comments.

Declaration of interests

DI has undertaken consulting work for several pharmaceutical companies including Eli Lilly, Merck Serono, GlaxoSmithKline, and UCB Pharma. The support offered is made available to a local arthritis charity. LL and GM declare that they have no competing interests.

References


