Systemic lupus erythematosus

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Systemic lupus erythematosus is an autoimmune connective-tissue disorder with a wide range of clinical features, which predominantly affects women, especially from certain ethnic groups. Diagnosis is based on clinical assessment supported by investigations, including the finding of autoantibodies. Treatments range from antimalarial agents to corticosteroids and immunosuppressive agents. This Seminar draws attention to advances in the epidemiology, genetics, cardiovascular risks, lupus nephritis, CNS disease, the antiphospholipid syndrome, assessment of disease activity and damage, and pregnancy related and quality of life issues. New therapeutic approaches, such as biological agents and mycophenolate mofetil, will also be discussed.

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Systemic lupus erythematosus is a multisystem, autoimmune, connective-tissue disorder with a broad range of clinical presentations. There is a peak age of onset in young women between their late teens and early 40s and women to men ratio of 9:1. Ethnic groups, such as those with African or Asian ancestry, are at greatest risk of developing the disorder, which can be more severe than in white patients. This disorder is a chronic illness that can be life threatening when major organs are affected, but more commonly results in chronic debilitating ill health. Factors such as sunlight and drugs could trigger the disorder, but no one cause has been identified and systemic lupus erythematosus has a complex genetic basis.

Epidemiology

The most striking studies of the epidemiology of lupus examined the development of autoantibodies years before the onset of clinical features of lupus and antiphospholipid syndrome.[2,3] The investigators used the US Department of Defense serum repository, which contains about 30 million samples from service personnel taken at baseline and on average alternate years. They identified 130 individuals with systemic lupus erythematosus and reported that 72 developed autoantibodies to DNA on average 2·7 years and up to 9·3 years before diagnosis. The researchers also described the frequency of other autoantibodies, such as antinuclear, antiRo, antiLa, antiSm, antiRNP,[2] and antiphospholipid antibodies[3] before the development of clinical disease. Antinuclear antibodies arose earlier than antiDNA antibodies and several of these patients had a rise in the antiDNA titres just before diagnosis. AntiSm and antiRNP antibodies appeared shortly before diagnosis, suggesting a peak of autoimmunity, resulting in clinical illness. The data also suggest that autoantibodies alone do not necessarily result in clinical disease and that other factors, possibly genetic and environmental, could be important. We might in the future be able to predict the onset of clinical features of lupus by clinical assessment and monitoring of the development of various lupus autoantibodies.

The frequency of lupus could be increasing because milder forms of the disease are being recognised. For example, Uramoto and co-workers[4] examined the incidence of the disorder in Rochester, MN, USA, and noted that it had more than tripled from 1·51 per 100 000 in the 1950–79 cohort to 5·56 per 100 000 between 1980 and 1992. In this study, although survival in the later cohort was worse than in the general population, there were clear improvements in survival rates over the 1950–79 cohort.[4] Trager and colleagues[5] suggested that patients with lupus nowadays could have a milder form of the disease and a better chance of survival than patients described several decades ago, probably because of an earlier diagnosis of milder disease. However, despite these improvements in survival, fatigue and other quality of life measures might not have improved.

A review of 32 studies has summarised the incidence and prevalence of systemic lupus erythematosus in several countries and documented the increased disease burden, especially in non-white populations (table).[6] Although there was wide variation in the prevalence of lupus worldwide, the highest prevalences were reported in Italy, Spain, Martinique, and the UK Afro-Caribbean population.

This disease is more common in women with African ancestry but is thought to be rare in west Africa, suggesting that environmental factors can contribute to the development of lupus in women whose ancestors migrated from that region. However, when women who had recently migrated from west Africa were examined, the prevalence of lupus was similar to that seen in Afro-Caribbean women but was much lower in European women.[7] These data

Search strategy and selection criteria

We used PubMed to access articles on systemic lupus erythematosus and the antiphospholipid syndrome, covering January, 2001, until August, 2006, supplemented with review articles. (*The Lancet* published a Seminar on this subject in 2001).[1] Search terms we used were "systemic lupus erythematosus", "antiphospholipid syndrome", "lupus nephritis", "central nervous system disease in lupus", and "fatigue". Articles were selected according to their effect on clinical practice. We have not attempted to give a comprehensive review of all the possible aspects of lupus—rather, we have focused on areas in which there have been substantial advances in the understanding of the pathogenesis of lupus and in which there have been major new developments in treatment.

suggest that systemic lupus erythematosus is fairly common in west Africa and that there is a genetic basis for the higher risk of lupus in these women.

Pathogenesis

The pathogenesis of lupus remains unclear, although the notion of apoptosis goes some way to explain how the immune system might recognise predominantly intracellular antigens. Autoantigens are released by both necrotic and apoptotic cells. Defects in the clearance of apoptotic cells have been described in this disorder and these defects could lead to aberrant uptake by macrophages, which then present the previously intracellular antigens to T and B cells, thus driving the autoimmune process.[8] Further studies have expanded these ideas and examined possible defects in the clearance of apoptotic bodies, including complement deficiencies, defects in macrophage handling, and presentation of these antigens to the immune system.[8]

Cytokine patterns might also be important in the pathogenesis of lupus. Investigations[9] have drawn attention to the overexpression of the type I interferon pathway in patients—the so-called interferon signature. A large study[10] has convincingly shown an association of a common interferon regulatory factor 5 (IRF5) haplotype, driving enhanced expression of multiple unique isoforms of IRF5 as an important genetic risk factor for the disease.

Abnormal signal transduction could also be important in the pathogenesis of systemic lupus erythematosus. For example, decreased expression of T-cell receptor ζ chain and protein kinase C □, decreased protein kinase C-dependent protein phosphorylation, impaired translocation of nuclear factor κB p65, and decreased production of interleukin 2, have all been described in T cells from patients with this disorder.[11]

	Incidence (per 100 000 per year)	Prevalence (per 100 000)
USA		
All races	5·1	52·2
White	1·4	7·4
Black	4·5	19·5
Puerto-Rican	2·2	18·0
Canada		
White	1·6	20·6
First Nations	4·7	42·3
Finland	NA	28·0
France	5·0	40·0
Iceland	3·3	35·9
Italy	NA	71·0
Northern Ireland	NA	25·4
Spain		
All races	NA	91·0
White	2·2	34·1
Sweden	4·7	42·0
UK		
All races	3·8	26·2
White	3·0	20·5
Asian	10·0	47·8
Chinese	NA	92·9
Afro-Caribbean	21·9	159·4
Australia		
White	NA	19·3
Aboriginal	11·0	63·1
Japan	2·9	28·4
Martinique	4·7	64·2

NA=data not available. Adapted from reference 6 with permission from Sage Publications.

Table: **Incidence and prevalence of systemic lupus erythematosus worldwide**

Genetics

Genetic susceptibility to lupus is inherited as a complex trait and studies have suggested that several genes could be important. In particular, an interval on the long arm of chromosome 1, 1q23–24, is linked with systemic lupus erythematosus in many populations. Clinically, active disease is accepted to be characterised by increased erythrocyte sedimentation rates but normal C-reactive protein (CRP) concentrations. CRP, complement, and serum amyloid P protein are important in clearing apoptotic cell debris, and the genes for CRP have been mapped to chromosome 1, 1q23–24, the so-called pentraxin locus. Russell and colleagues[12] examined the inheritance of polymorphisms at the pentraxin locus in a family-based investigation and reported strong linkage disequilibrium within each of the CRP and serum amyloid P genes. The researchers showed that an allele of CRP 4 was associated with the disorder. Furthermore, two haplotypes were significantly associated with reduced basal CRP expression—CRP 2 and CRP 4. An allele of CRP 4 was associated with antinuclear antibody production. Thus, the researchers proposed a genetic explanation of the link between low CRP concentrations and antinuclear autoantibody production, and the contribution these make to the development of lupus in human beings.

Another large study of individuals and multicase families with lupus[13] suggested that a single nucleotide polymorphism within the programmed cell death 1 gene (PDCD1) is associated with the development of the disease in both European and Mexican populations. The researchers showed that the associated allele of this single nucleotide polymorphism alters a binding site for a transcription factor located in an intronic enhancer, suggesting a mechanism through which it can contribute to the development of systemic lupus erythematosus.

Environmental factors

Sunlight is the most obvious environmental factor that can exacerbate the disease (panel 1). Other factors have been considered and crystalline silica was the focus of studies from southeast USA, where occupational

Panel 1: **Factors associated with development of systemic lupus erythematosus**

- Sunlight
- Drugs: >100 described in association with drug induced lupus
- Epstein-Barr virus
- Abnormalities of apoptosis
- Abnormal signal transduction: toll like receptors
- Cytokine patterns: interferon signature; decreased interleukin 2 from T cells
- Genes: CRP and serum amyloid P genes, FcγR receptors, programmed cell death
- Occupational exposure: silica, pesticides, mercury

exposure was postulated as a risk for development of lupus.[14] A case control study showed that more patients than controls (19% *vs* 8%) had a history of medium-level or high-level silica exposure from farming or trades. This finding suggests that such exposure could be associated with the development of the disorder in a proportion of individuals, although occupational exposure can often be difficult to quantify accurately. A further study[15] showed links between the disorder and self-reported occupational exposure to mercury in agricultural workers who mix pesticides and among dental workers, although the actual number exposed to mercury was small. Unlike with scleroderma, though, there was no association with solvent use.

Epstein-Barr virus (EBV) has also been identified as a possible factor in the development of lupus. This virus can reside in and interact with B cells. Gross and colleagues[16] reported a high frequency of B cells infected with EBV in lupus patients compared with controls, and these infected cells were predominantly memory B cells. There was no relation with immunosuppressive therapy, and patients with active lupus flares had more infected cells than did patients with quiescent disease. Although other work has suggested a causative role for EBV in systemic lupus erythematosus, Gross and colleagues are more cautious, and despite their findings of increased frequencies of infected cells, increased viral loads, and viral gene expression, they have not interpreted this as directly implicating this virus in the development of systemic lupus erythematosus, arguing that the immune dysregulation of the disorder could also result in aberrant EBV expression.[16] By contrast with this result, investigations in a mouse model[17] show that direct introduction of the whole virus nuclear antigen 1 protein can elicit IgG antibodies to Sm and to double-stranded DNA, thus lending support to an assumed role for EBV in the development of lupus. The paradox remains that although 90% of the adult population are infected with EBV, the prevalence of systemic lupus erythematosus remains low, which emphasises the multifactorial nature of the pathogenesis of this disorder.

Hormonal factors

Systemic lupus erythematosus is a disease affecting women of childbearing age and there have been many anecdotal reports of exogenous oestrogens exacerbating lupus or increasing the risk of developing this disorder. Oral contraceptive use in the Nurses Health Study[18] was associated with a slightly increased risk of disease with a relative risk for users versus never users of 1·9. Hormone replacement therapy (HRT) has been associated with an increased risk of systemic lupus erythematosus,[19,20] although another study failed to show any increased risk.[21] Several studies have suggested that HRT is unlikely to increase the risk of flares, although these studies in general have been small retrospective case series.[22] The SELENA trial[23] randomly assigned women with the disorder to receive either HRT or a placebo. Although women given hormone treatment had no increase in major flares, they had more mild to moderate flares than did those on placebo. Several women, including one in the placebo group, developed thrombotic events. The pendulum has swung against the long-term use of HRT, although it might still have a use for short periods in women with systemic lupus erythematosus, who are antiphospholipid antibody negative and have severe menopausal symptoms. This investigation will inform patients and clinicians of the potential risks and confirms the view that HRT is contraindicated in women with antiphospholipid antibodies.

The use of the combined oestrogen-containing oral contraceptive pill has been discouraged in lupus patients after anecdotal reports of serious disease flares. This recommendation seemed reasonable since systemic lupus erythematosus has a hormonal component and is a disorder of young women. Two randomised controlled trials have investigated the use of the contraceptive pill in women with lupus. Petri and colleagues[24] randomly assigned 183 women with inactive or stable low-grade lupus activity to either a combined low-dose oestrogen-containing oral contraceptive pill or a placebo for 1 year. All participants practised other effective birth control methods. No differences in the rates of severe or mild to moderate disease flares were reported in either treatment group and the researchers suggested that this type of contraception could be considered in women with lupus who need effective birth control, especially when receiving cytotoxics, for amelioration of menstrual disease flares, and protection against steroid-related bone loss.

Sanchez-Guererro and co-workers[25] also addressed this question. They randomly assigned 162 women with lupus to either combined oral contraceptive pills, progestagen-only pills, or a copper intrauterine device. At the end of 1 year, there were no differences in disease activity scores or flare rates. This study included asymptomatic patients with antiphospholipid antibodies and four (two in each of the hormone groups) had venous thrombotic events. There was a higher infection rate in women assigned to the intrauterine device.

These studies provide some reassurance for lupus patients with mild, stable forms of the disease, who are antiphospholipid antibody negative and wish to consider the use of the oral contraceptive pill. However, the findings of both studies emphasise the thrombotic risk inherent in lupus patients, even if antiphospholipid antibodies are absent.

Cardiovascular risk

Over the past 5 years there has been an increase in published work assessing the prevalence and risk factors for the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. Three case-control studies[26–28] confirmed that atherosclerosis develops prematurely, independently of traditional risk factors for cardiovascular disease. Lupus itself seems to be a risk factor for the development of atherosclerosis, and a reasonable theory suggests that inflammatory disease activity over long periods results in endothelial and vascular damage, which sets the scene for atherosclerosis. In addition to intensive management of disease activity, aggressive risk factor reduction will be essential to improving outcome. Wajed and co-workers[29] have suggested guidelines for controlling risk factors and they propose that this disorder should be regarded as a coronary artery disease equivalent, in much the same way as is diabetes mellitus.

The contribution of antiphospholipid antibodies to accelerated atherosclerosis in systemic lupus erythematosus remains unclear. Although there is persuasive experimental evidence to lend support to a role for these autoantibodies, some case-control and epidemiological studies have not reported any relation. The role of corticosteroids also remains unclear. Although high-dose corticosteroids are clearly associated with glucose intolerance, hypertension, central obesity, and dyslipidaemia, low-dose corticosteroids and other therapies, such as antimalarials and immunosuppressives, could actually reduce the risk of atherosclerosis by keeping vascular damage to a minimum.[26]

Although the risk of cardiovascular events in patients with lupus is substantially increased, the total number of patients with events is fairly low considering that lupus is much less common than is diabetes mellitus. Svenungsson and co-workers[30] showed that lupus patients with a previous cardiovascular event had a distinct pattern of risk factors, including increased carotid intima-media thickness, raised concentrations of circulating oxidised LDL, triglycerides, and lipoprotein (a), raised α1-antitrypsin and homocysteine concentrations, and decreased HDL cholesterol. Patients were more likely to have the lupus anticoagulant, osteoporosis, and higher cumulative prednisolone doses than were patients with systemic lupus erythematosus but no previous cardiovascular event. In addition to antiphospholipid antibodies and lupus itself as risk factors, variant alleles of mannose-binding lectin are associated with both an increased risk of lupus and arterial thrombosis in patients with lupus.[31]

Lupus nephritis

The assessment and management of lupus nephritis has seen major advances over the past 5 years. WHO's classification for lupus nephritis has been updated to allow more accurate descriptions of renal histopathological specimens by the International Society of Nephrology and the Renal Pathology Society (figure).[32] These descriptions allow better communication between pathologists translating static images from histology slides into meaningful descriptions of the huge variations in biopsy appearances for clinicians.

The present standard of care with monthly high-dose intravenous cyclophosphamide has been challenged on several fronts. The so-called US National Institutes of Health (NIH) regimen of high-dose intravenous cyclophosphamide pulses once a month for 6 months, followed by once every 3 months for up to 2 years was developed in the 1970s and 1980s and became widely established as the treatment of choice for severe lupus nephritis (although this approach was never approved by the US Food and Drug Administration). Over the past 15 years, alternative ways of administering cyclophosphamide in much lower doses for shorter periods than in the NIH regimen have emerged. Houssiau and co-workers[33,34] in the European Lupus Nephritis Trials group completed a randomised controlled trial of the NIH regimen versus high-dose intravenous cyclophosphamide pulses once a month for 6 months, followed by two pulses 3 months apart and azathioprine with six fixed-dose 500 mg pulses of cyclophosphamide given every 2 weeks, followed by azathioprine. At long-term follow-up (6 years), there were no differences in the rates of end-stage renal failure or doubling of serum creatinine, and there was a non-significant trend to a lower risk of infections in patients assigned to the low-dose cyclophosphamide regimen. Although underpowered to show true equivalence, these investigations confirm a move away from the long-term use of high-dose cyclophosphamide, especially in view of the undoubted risks of infection and ovarian toxicity with the NIH regimen.

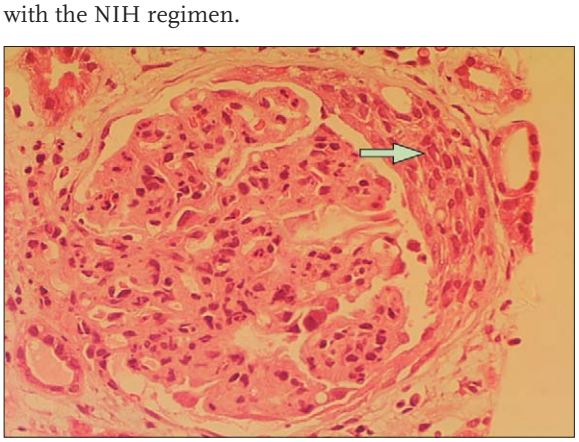

Figure: **Diffuse proliferative lupus glomerulonephritis with epithelial crescent (arrow)**

However, there is still a need for alternative induction therapies for lupus nephritis. Chan and colleagues[35] undertook a randomised controlled trial of mycophenolate mofetil versus oral cyclophosphamide for 1 year followed by azathioprine in patients with proliferative lupus nephritis. Although numbers were small, this work strongly suggested that mycophenolate mofetil could be used in induction therapy with corticosteroids, with substantial improvements in safety compared with cyclophosphamide. A follow up study of these patients confirmed this trend with similar relapse-free survival between the mycophenolate mofetil and cyclophosphamide groups.[36] Ginzler and colleagues[37] extended these data with a 24-week randomised non-inferiority trial of mycophenolate mofetil versus six high-dose intravenous cyclophosphamide infusions 1 month apart. They showed, using strict criteria for complete and partial remissions, that mycophenolate mofetil was better than intravenous cyclophosphamide and withdrawal rates were higher in the cyclophosphamide group. There were fewer severe infections but more diarrhoea in the mycophenolate mofetil group than in those on cyclophosphamide.

A further controlled trial addressed the question of maintenance therapy for lupus nephritis. Contreras and colleagues[38] treated 59 patients with lupus nephritis with NIH-style intravenous cyclophosphamide infusions once a month for 6 months and then randomly assigned the patients to one of three maintenance therapies—(a) continuing quarterly intravenous cyclophosphamide, (b) azathioprine, or (c) mycophenolate mofetil, for 1–3 years. The patients assigned to long-term intravenous cyclophosphamide therapy fared very poorly by any criteria, compared with those assigned mycophenolate mofetil or azathioprine, both in terms of outcome and toxicity. These studies all suggest that the era of high-dose, long-term, intravenous cyclophosphamide for induction or maintenance therapy of lupus nephritis is drawing to a close.

Central nervous system lupus

CNS disease in lupus remains challenging in terms of pathogenesis, assessment, and treatment. A study by DeGiorgio and colleagues[39] showed that antiDNA antibodies recognise a pentapeptide that is also present in the extracellular domain of murine and human N-methyl-D-aspartate (NMDA) receptor subunits NR2a and NR2b, which bind the neurotransmitter glutamate. Furthermore, they showed that the NR2 receptor is recognised by both murine and human antiDNA antibodies and that these crossreactive antiDNA antibodies can induce neuronal apoptosis. In an extension of their work, they showed that cerebrospinal fluid from a patient with systemic lupus erythematosus and progressive cognitive decline contained these antibodies and also mediated neuronal death via an apoptotic pathway. Thus, lupus antibodies can crossreact with DNA and NMDA receptors, gain access to cerebrospinal fluid, and can result in abnormalities of the CNS.

The diagnosis of CNS lupus remains clinical, backed up by investigations that exclude other causes of the symptom complex. Imaging studies have in general been disappointing, with no one imaging method able to provide conclusive evidence for CNS lupus. More advanced techniques, such as magnetic resonance spectroscopy, might prove useful by identifying drops in N-acetylaspartate concentrations and rises in myoinositol concentrations in white matter of normal and abnormal appearance in patients with neuropsychiatric lupus.[40]

The American College of Rheumatology (ACR) classification criteria for CNS lupus has changed substantially—from seizures and psychosis to 19 different syndromes that are classifiable.[41] An emerging notion is the distinction between CNS manifestations due to lupus and those caused by the antiphospholipid (Hughes') syndrome.[42] A range of neuropsychiatric manifestations attributable to this syndrome have been described, including strokes, seizures,[43] movement disorders, transverse myelopathy,[44] demyelination syndromes, transient ischaemic attacks, cognitive dysfunction, visual loss, and headaches (including migraine).[45] Sanna and colleagues[45] used the ACR nomenclature to assess the prevalence of CNS disorders in a large cohort of patients with systemic lupus erythematosus and reported that cerebrovascular disease, headaches, and seizures were correlated with antiphospholipid antibodies. The differential diagnosis between multiple sclerosis and demyelination associated with antiphospholipid syndrome can be difficult on imaging grounds,[46] although electroencephalography can offer some indications of cerebrovascular insufficiency.[47]

Seizures are an important feature in disease diagnosis—for example, seizures in patients with lupus are more likely to be associated with antiphospholipid syndrome than with the overdiagnosed cerebral vasculitis. The range of seizure disorder is wide. A study of more than 500 patients with this syndrome suggested that epilepsy was more common in patients with both systemic lupus erythematosus and antiphospholipid syndrome than in patients with lupus alone. The study also suggested that epilepsy was correlated with focal ischaemic events (strokes or transient ischaemic events) and amaurosis fugax and that patients with antiphospholipid syndrome and epilepsy had a higher frequency of cardiac valvular changes and livedo reticularis than did those without epilepsy.[41] Headaches and seizures improve after anticoagulation is started, lending support to a thrombotic basis for these clinical features.[48]

Quality of life issues

Although survival has greatly improved in patients with lupus over the past 50 years, substantial challenges remain in improving quality of life for these patients. Indeed, actual measurement of quality of life has not been straightforward because there are very few validated instruments, which is an area that is being addressed.[49]

Fatigue severely affects quality of life. Factors contributing to fatigue remain complex and include depression, pain, poor sleep quality, poor physical fitness, perceived social support, and disease activity (though this factor remains controversial).[50] Two clinical trials of supervised exercise programmes showed improvement in terms of aerobic capacity, quality of life, and depression. One study showed improvements in fatigue without causing disease flares, although the beneficial effects disappeared on stopping the exercise programmes.[51,52]

Pregnancy

Overall, pregnancies for patients with lupus have a greater risk of spontaneous miscarriage, preeclampsia, intrauterine growth restriction, fetal death, and preterm delivery. The degree of risk depends on several factors at the time of conception, including the presence of lupus nephritis, hypertension, antiphospholipid antibodies, and active disease. Pulmonary hypertension arises in up to 14% of patients with lupus and even mildly raised pulmonary artery pressures can be seen in 37% of patients.[53] In pregnancy, raised pulmonary artery pressures confer a high risk of maternal death and these rare patients should be counselled accordingly and managed in specialist multidisciplinary units.

Although there has been some debate in published work as to whether flares in lupus activity actually occur during pregnancy, the present consensus is that pregnancy could exacerbate lupus activity.[54] Flares arise in about 30–60% of pregnant patients with lupus, and flares in renal disease activity are more common in those who had active disease at conception than in those in remission.[55] Pregnancy outcome is especially affected by renal disease, and even inactive renal lupus is associated with increased risk of fetal loss, pre-eclampsia, and intrauterine growth restriction. For example, Tandon and colleagues[56] suggested that, during pregnancy, patients with systemic lupus erythematosus and renal disease showed changes in renal disease activity and deterioration in renal function that were similar to those in non-pregnant patients with lupus nephritis. Another study[57] showed that hypertension and pre-eclampsia were much more common in patients with pre-existing proliferative (WHO class III and IV) lupus nephritis than in those with histologically milder disease (WHO class II and V), with substantially lower birthweights in the proliferative nephritis group.

Hydroxychloroquine should not be stopped in early pregnancy, because this could precipitate a flare, and its long half-life means the fetus would continue to be exposed to the drug for several weeks, even after discontinuation. Investigations in pregnant women exposed to hydroxychloroquine have shown that the congenital abnormality rate is no higher than that of the background population.[58]

Studies of experimental antiphospholipid syndrome suggest that complement system activation, especially C_3 and C_5, is an important mechanism of antiphospholipid-induced pregnancy loss.[59] This work also suggests that heparin prevents antiphospholipid-induced pregnancy loss by inhibiting C_3 and C_5 activation rather than its anticoagulant effects.[60] C_3 and C_5 activation might amplify the procoagulant effects of antiphospholipid antibodies and targeting C_3 and C_5 could, therefore, prove useful for future therapy.

Antiphospholipid syndrome (Hughes' syndrome)

The description of the antiphospholipid syndrome in 1983 has, arguably, proved to be the pivotal advance in the management of lupus over the past half-century. The ramifications of the syndrome extend beyond lupus, to all disciplines of medicine. The classification criteria for this syndrome have been updated to include manifestations not previously classifiable.[61] A description of the clinical features of 1000 patients with the syndrome remains the largest such series.[62] The study documents the wide range of clinical features arising from thrombosis in any organ system and confirms the importance of livedo reticularis as a marker. The catastrophic antiphospholipid syndrome was seen in 0·8% of patients and remains a serious complication with a poor outlook for patients. Classification criteria for catastrophic antiphospholipid syndrome have been validated and a worldwide register set up to record clinical data for these rare patients to analyse treatment and outcomes.[63] The data suggest that plasma exchange, corticosteroids, and intravenous immunoglobulin could be helpful, but immunosuppression, especially with cyclophosphamide, increases mortality.[63]

Primary antiphospholipid syndrome rarely progresses to systemic lupus erythematosus. Only 8% of 128 patients, who were followed up for about 9 years, developed lupus, and a positive Coombs test was a clinically significant predictor of progression.[64] Antiphospholipid syndrome complicating systemic lupus erythematosus substantially increases the risk of damage and death.[65] The range of clinical features of antiphospholipid syndrome continues to broaden, with descriptions of renal artery stenosis,[66] metatarsal fractures,[67] avascular necrosis,[68] and abnormalities of vascular function.[69] One of the features distinguishing antiphospholipid syndrome from other coagulopathies is the tendency to develop heart valve disease, sometimes progressing rapidly to valve replacement.[70]

A major focus of research is the relation of antiphospholipid syndrome to accelerated atheroma, with investigations showing cross-reactivity of antiphospholipids with oxidised LDL, and early signs of arterial disease in antiphospholipid-positive individuals.[69,71] The relevance of these findings has not been lost on those studying the high cardiovascular disease mortality in patients with systemic lupus erythematosus—George and Shoenfeld[72] have termed antiphospholipid syndrome as the "crossroads of autoimmunity and atherosclerosis".

Pulmonary hypertension is also a feature of lupus that is associated with antiphospholipid syndrome.[73,74] Progress has been made in identifying patients with pulmonary hypertension associated with autoimmune rheumatic diseases. Treatment with agents such as sildenafil and bosentan, as well as the more established prostacyclin analogues, is promising.[75]

Although classification criteria demand positive antiphospholipid tests, increasing numbers of patients are seen in whom classic features of antiphospholipid syndrome are present but in whom comprehensive blood testing is negative.[76] Although there are several possible reasons for this seronegative syndrome (including wrong diagnosis), the notion is important and certainly leaves room for further developments in blood testing.[77]

Treatment of antiphospholipid syndrome remains controversial, especially in terms of the amount of anticoagulation required to prevent recurrent thromboses. Two prospective studies[78,79] showed that high-intensity anticoagulation, with international normalised ratios (INRs) above 3·0, were no better in prevention of recurrent thromboses than conventional therapy, with INRs of 2·0–3·0, contradicting previous retrospective data. A further study[80] added impetus to this research by suggesting that positive baseline antiphospholipids in stroke patients did not predict subsequent cerebrovascular occlusive events or a differential response to aspirin or warfarin therapy. The researchers even went as far as suggesting that routine screening for antiphospholipids in these patients was not warranted. The investigation has been criticised on several grounds, not least being the fact that the study was not originally designed to address the issue of screening and that only one baseline measurement of antiphospholipids (including low titre values) was used. Most clinicians still regard antiphospholipid testing in young stroke patients as being essential.

New treatments

Since 2001, there have been major advances in the treatment of this disorder. Newer, low dose cyclophosphamide regimens have already been described and biological agents are now having an effect.

Rituximab is a chimeric human-murine monoclonal antibody directed against CD20 on B cells and their precursors but not against plasma cells, which do not have this antigen. Rituximab has been widely used in the management of lymphoma and is fairly safe and well tolerated. There is increasing evidence showing substantial and longlasting remissions in patients with lupus, who were previously unresponsive to conventional and novel immunosuppressive agents, such as mycophenolate mofetil. Among the first to undertake open work in lupus were Leandro[81] and Anolik[82] and their colleagues and there have been many small open-label investigations since then. The overwhelming consensus is that rituximab has the potential to produce long remissions after only two to four infusions. There are various protocols in use that combine rituximab with intravenous cyclophosphamide and methylprednisolone, and we do not know whether maintenance immunosuppression is needed after rituximab to prevent B-cell reaccumulation and possible subsequent disease flares. There are several trials in progress to address these issues. The precise mechanism of action of rituximab remains unclear.

The idea that B cells are depleted, resulting in reduced autoantibody production is too simplistic. Vigna-Perez and colleagues[83] have not only confirmed the effectiveness of rituximab in resistant lupus nephritis but also provided insights into potential mechanisms of action. For example, although there were few changes in complement or autoantibody concentrations, there were substantial increases in the concentrations of different CD4 regulatory T cells and increased T-cell apoptosis at day 30 after rituximab. This result suggests that rituximab has effects on the interaction between regulatory T cells and B cells that extend beyond simple B-cell depletion.[83] Humanised monoclonal anti-B-cell antibodies are in clinical trials and Dorner and colleagues'[84] findings suggest that epratuzumab, a fully human antiCD22 monoclonal antibody, is safe in patients with lupus and is able to reduce disease activity effectively in the short term.

Intravenous immunoglobulins are increasingly being used in the treatment of resistant lupus, although there are no large randomised trials. These drugs have a role in patients who have concomitant infection and active lupus in whom immunosuppression is risky, and they have also been used in the treatment of a wide range of clinical manifestations in systemic lupus erythematosus patients.[85]

Autologous stem-cell transplantation has been viewed with some caution in the management of severe lupus on account of the substantial treatment-related morbidity and mortality. However, an investigation[86] of 50 severely affected patients undergoing autologous non-myeloablative haemopoietic stem-cell transplantation drew attention to significant clinical improvements, with a treatment-related mortality of 4% and a 5-year survival of 84%. A previous report from the same group[87] suggested that patients with antiphospholipid syndrome were able to discontinue warfarin, and most remained thrombosis free after stem-cell transplantation. There is a range of new treatments in clinical trials or animal studies and these are summarised in panel 2.

Assessment of disease activity and damage

The assessment of lupus in clinical trials has been dependent on several disease activity scoring systems, which usually provide one numeric value. The British Isles Lupus Assessment Group (BILAG) is useful in clinical trials because it describes disease activity on the basis of the physician's intention to treat the patient,

Panel 2: **New treatments for systemic lupus erythematosus**

Anticytokine therapies
- AntiTNFα
- Anti-interleukin-1-receptor: anakinra
- Anti-interleukin 10
- Anti-interleukin 6 receptor
- Anti-interferon alpha
- Anti B-lymphocyte stimulator (Blys)

Costimulation inhibition
- AntiCD154
- CTLA4Ig: abatacept

B-cell anergy
- LJP 394: abetimus

B-cell depletion
- Anti-CD20: rituximab
- Anti-CD22: epratuzumab

Other techniques
- Immunoadsorption
- AntiC5a
- T cell vaccination
- ζ chain transfection
- Peptide therapies: edratide targeting antiDNA idiotypes

and provides a clear picture of affected organs and systems. It has undergone revision and is being validated.[88] Other disease activity scoring systems have been updated, including the systemic lupus erythematosus disease activity index 2000 (SLEDAI 2K) and an adjusted mean SLEDAI-AMS that describe disease activity over time.[89,90]

Damage describes irreversible events resulting from lupus disease activity and its treatment. The link between damage and an increased risk of morbidity and mortality is now clear. A study that draws attention to this association is that of Ruiz-Irastorza and colleagues,[65] who examined the contribution of antiphospholipid syndrome to damage and mortality. In 202 patients with systemic lupus erythematosus, those with antiphospholipid syndrome had a higher damage score than those who did not, which was mostly attributed to damage resulting from arterial thromboses. Even patients without antiphospholipid syndrome who had high damage scores were at greater risk of death, and several investigations have assessed predictors of outcome, including damage. For example, Stoll and colleagues[91] concluded that death and the long-term accumulation of damage is a function of total disease activity over time and especially correlated with major flares, as assessed by the BILAG index.[91] Clearly, clinicians have to try, as far as possible, to achieve disease remission, although studies emphasise the inadequacies of present treatments in achieving this aim, and long-lasting disease remission is quite rare.[92]

Another important outcome measure is the risk of cancer associated with lupus. This measure has been a controversial issue, but a large study of 9547 patients from 23 centres confirmed an increased risk of non-Hodgkin lymphoma in patients with systemic lupus erythematosus.[93] It remains to be seen whether treatment with immunosuppressive agents can increase this risk, but older work has not lent support to a strong link between cancer and immunosuppressive therapy, except for the well known risk of bladder cancer with long-term cyclophosphamide use.

Conclusion

The next 5 years should see a consolidation of therapies, such as low-dose cyclophosphamide regimens, mycophenolate mofetil, and rituximab as well as the emergence of many potentially useful and highly targeted treatments. The major remaining challenges include improving the quality of life for patients with lupus, by keeping corticosteroids, infections, and fatigue to a minimum and reducing cardiovascular risk, which still claims substantial loss of life.

Conflict of interest statement

DD and GRVH have received honoraria from Aspreva. DD is involved in clinical trials led by Aspreva, UCB Pharma, Immunomedics, and TEVA Pharmaceuticals.

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