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Newsletter

New insights into SLE
(Systemic Lupus Erythematosus)

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Introduction

Lupus is a disease caused by a disorder of the immune system. Its pathophysiological mechanisms, which include genetic, immunological and environmental factors, remain poorly understood.

This is a rare disease: e.g. in the United States, its prevalence is between 15 and 50 per 100,000 inhabitants and its incidence is between 5 and 10 new cases per year for 100,000 inhabitants. It mainly affects women (ratio 9:1 Female vs Male) and in particular young women, aged from 25 to 35; the age profile has been changing, however, over the last few years, with more women being affected after the age of 50. Lupus patients have a ten year survival rate of over 90%, thanks to therapeutic progress and earlier diagnosis.

On the other hand, the treatments available have side effects and morbidity is high. Certain criteria are associated with a poor prognosis: lupus is more serious, for example, in men than in women; children with the disease develop more severe complications in adulthood.

Lupus is an autoimmune disease (AID) characterised by an abnormal immune reaction of the body against itself: the immune system, which is supposed to defend the body against external aggression turns on the body's own tissues. AIDs are subdivided into organ-specific, or localised and systemic, which can affect all the organs; lupus is the prototype of the systemic category, which also includes rheumatoid arthritis, Sjögren's syndrome, anti-phospholipid antibody syndrome, systemic sclerosis, inflammatory myopathy, etc. The organs mainly affected are the skin, the joints, the kidneys and the heart. With the exception of vasculitis (inflammation of the blood vessels), systemic AIDs occur under the combined effects of genetic predisposition, environmental factors and the failure of the immune regulation system.

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The different forms and clinical signs of lupus

Lupus is a chronic disease, which occurs in flares. Its clinical expression takes many forms and it may begin with any of the range of symptoms.

The disease has benign and serious forms. The more minor manifestations, such as the cutaneous and articular forms and minor visceral symptoms are not in most cases the cause of early mortality, although they can be very incapacitating. The kidneys (class I, II and V lupus nephritis in the WHO classification), heart (pericarditis in particular) and lungs (pleurisy) are affected in the moderate forms of the disease. The more serious forms, which cause early death, include lupus nephritis (classes III, IV and VI in the WHO classification), neuropsychiatric lupus, cardiovascular conditions (myocarditis for example), thrombo-embolism (pulmonary embolism) and iatrogenic complications (infections, cancer, lymphoma).

The **ACR** (American College of Rheumatology) has listed «eleven criteria of lupus», which are used throughout the world to diagnose the disease. Among the eleven criteria, the first seven are clinical, four of them concerning the skin and the mucous membranes (malar rash, discoid rash, photosensitivity, oral ulcers or nasopharyngeal ulcers). The last four are biological.

A formal diagnosis of lupus is made if at least four of the eleven criteria are met.

The ACR criteria of lupus

Clinical criteria		Biological criteria	
1	Malar rash	8	Proteinuria > 0.5 g/24h or cellular casts in the urine
2	Discoid rash	9	Haemolytic anaemia or cytopenia (leukopenia < 4000/µL or lymphopenia < 1500/µL or thrombopenia < 100 000 /µL)
3	Photosensitivity	10	Antibodies to native DNA or antibodies to Sm or false positive serological test for syphilis or abnormal level of antibodies to cardiolipin or presence of a circulating anticoagulant
4	Oral or nasopharyngeal ulcers	11	Positive antinuclear antibody test
5	Non-erosive arthritis		
6	Pleurisy or pericarditis		
7	Seizures or psychosis		

> 3 criteria: Lupus diagnosis

Source: Arthritis Rheum. 1997;40(9):1725

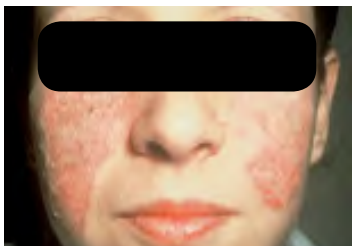
Benign forms of lupus

Cutaneous form

The term «lupus» comes from the Latin for «wolf» as the sufferer has a very characteristic facial rash supposedly resembling a wolf mask. When lupus is purely cutaneous, it can take three different forms: acute lupus (30 to 60% of cases) takes the form of a red, inflamed, painful rash that may affect the mucous membranes; it will flare up then clear without leaving any marks, unlike the subacute form (7 to 20%) which remains and whose lesions (on the face, trunk and limbs) can be distressing for patients. Finally, discoid or chronic lupus (15%) is similar to subacute lupus, but with a different clinical appearance (cf. photo opposite).

Chronic cutaneous lupus

Source: La Pitié-Salpêtrière Hospital



Within pure cutaneous lupus, the subacute and chronic forms generally remain non-systemic, whereas the acute forms have a tendency to evolve into the systemic form of the disease.

Articular manifestations

These affect 86% of patients, mainly in the form of arthralgia and arthritis: inflammation of the hands, wrists, ankles, knees and feet, usually with articular swelling, but without joint deformity or destruction. When the joints are affected, the issue is whether or not this is linked to a flare of disease or a complication arising from its treatment: e.g. septic arthritis, myositis, aseptic osteonecrosis, tendinitis.

Moderate and serious forms of lupus

Lupus nephritis

Lupus nephritis (involving the kidneys) concerns 30 to 60% of patients. Two thirds of cases occur during the first two years of the disease; they are very rare after the 5th year. These are the most severe forms and they require regular monitoring of renal function. Kidney biopsy is performed to determine the type of lupus nephritis. The WHO has identified six classes of lupus nephritis: classes III, IV and VI are the most severe.

Lupus nephritis: the six WHO classes	
Class I	Normal kidney
Class II	Mesangial proliferative lupus nephritis: a not very severe form, rarely develops to renal failure
Class III	Focal lupus nephritis with inflammatory infiltrates that can lead to renal failure
Class IV	Diffuse proliferative lupus nephritis, with inflammatory infiltrates that can lead to renal failure
Class V	Membranous lupus nephritis (no infiltrates): a form that is generally not very severe, but can progress over the long term
Class VI	Advanced sclerosis lupus nephritis

Neuropsychiatric symptoms

Lupus often affects the central nervous system: in 25 to 60% of sufferers. The clinical presentations are polymorphous: focal syndromes (hemiplegia, cranial neuropathy, myelitis, chorea associated with antiphospholipids), seizures (epilepsy), diffuse central nervous system lupus (lupus-related psychosis). Mood disorders are common: depressive syndrome, anxiety.

Antiphospholipid syndrome

Certain lupus patients may develop antiphospholipid syndrome (APS). Likewise, certain patients with APS can develop secondary lupus.

APS is characterised by the presence of clinical signs (vascular thrombosis, pregnancy morbidity) and biological signs, with the presence of at least one of the following antibodies: antiphospholipid antibody, lupus anticoagulant, anticardiolipin antibody, anti-β2-glycoprotein I antibody; the last three of these antibodies are all directed against cell membrane phospholipids. To diagnose APS, one clinical criteria and at least one biologic sign among these three antibodies, which may also overlap, must be present.

As well as vascular thrombosis, APS can also have cutaneous signs: livedo reticularis, cutaneous necrosis, subungual splinter haemorrhages, skin nodules. It is treated with long-term anticoagulants in patients who have already had thrombosis and in whom antibodies are present. Patients who have not yet had thrombosis are treated preventively with anti-platelet drugs, in small doses.

Cardio-pulmonary involvement

These conditions concern 30% of lupus sufferers (including pericarditis 24%, pleurisy 22%, AHT 14%, valvulopathy 6%, myocarditis 4%). Pulmonary embolism occurs quite frequently, but abnormalities of the pulmonary parenchyma and pleurisy are less common. In this case it is necessary to differentiate superinfection from pulmonary embolism.

These cases can involve pericarditis (quite often the initial presentation) and this affects about 25% of patients, but is treatable with corticosteroids. Other cardiac manifestations include Libman-Sachs endocarditis (linked to antiphospholipids and can lead to systemic embolism), valvulopathy, myocarditis (very rare), and thrombosis.

At the present time, there are no markers for predicting lupus flares or the long-term progression of the disease, but Lupus nephritis and central nervous system lupus remain the most severe forms.

Biological markers of disease activity and treatments

Non-specific markers

The non-specific markers are markers of inflammation. The main ones are ESR (sedimentation rate), fibrinogen, alpha-1-acid glycoprotein, CRP (C-reactive protein); the last should be treated with precaution as levels are not necessarily elevated in lupus, except in the case of serositis, pleurisy, pericarditis or synovitis. Other non-specific markers include: hypergammaglobulinemia, anaemia (inflammatory or autoimmune haemolytic), leukopenia (<4000/µL), lymphopenia (<1500/µL), creatinemia, proteinuria, CBEU (cytobacterio-logical examination of urine).

All these signs are common in the disease and are markers of activity.

Specific markers

Lupus is an autoimmune disease and several autoantibodies, specific markers, count among the criteria for the disease.

Anti-nuclear antibodies are directed against nuclear antigens, present in the cell nucleus. Anti-nuclear antibodies are tested for in almost all the auto-immune diseases: they are very sensitive, but not very specific. In lupus, they are present in 90 to 95% of patients. But they are also present in 45% of patients suffering from rheumatoid arthritis, 50% of patients suffering from systemic sclerosis, 55% of patients suffering from Sjögren's syndrome, and in all patients suffering from Sharp syndrome. The test is very sensitive: when there is an AID, there is almost always an anti-nuclear antibody. But they are also found in non-autoimmune systemic diseases: idiopathic pulmonary fibrosis (50%), myasthenia (50%) and in subjects aged over 70 (15%).

After detecting the presence of antinuclear antibodies, it is necessary to determine their antigen specificity, in other words to identify their targets. If the target is DNA, then it is the antibody ***to native or double-stranded DNA.*** This is the antibody most specific to lupus, and it is detected using the Farr assay or the Crithidia luciliae test. If it is soluble nuclear antigen, then we are dealing with ***the anti-ENA antibody*** (Extractable Nuclear Antigen), whose anti-Sm antibody is the most specific for lupus.

The complement is a very important biological marker. There are three common tests: C3, C4 and CH50. Complement C3 is a good marker of lupus as a drop in its level is quite specific to a high level of disease activity. It is used both for diagnosis and to monitor the disease.

Anti-nucleosome antibodies: this protein, which wraps around the DNA with a pearl necklace-like structure, is more of a marker of lupus activity than a way of diagnosing lupus. Similarly, anti-histone antibodies concern mainly patients with drug-induced lupus.

A wide range of treatments

A wide range of treatments are used: they range from no treatment to biotherapies. Between these extremes, the drugs prescribed include hydroxychloroquine and non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and immune suppressants (cyclophosphamide, mycophenolate mofetil, Methotrexate©).

In cutaneous and articular lupus, the standard treatment is hydroxychloroquine; NSAIDS may also be given. If this treatment is insufficient, corticosteroids such as Prednisone© are added (in particular when the patient has pericarditis or pleurisy), at moderate doses. As soon as possible, the cortico-steroids are reduced in order to avoid side effects; at the same time the bones are protected with anti-osteoporosis treatments. The hydroxychloroquine/NSAID/corticosteroid combination may be replaced by hydroxychloroquine/AINS/ Methotrexate© to control the articular disease. Hydro-xychloroquine is always a first-line treatment in lupus: it is effective on the skin and the joints and helps to prevent other systemic manifestations; it also seems to have an anti-platelet aggregation effect, which can be useful in patients susceptible to thrombosis.

In severe lupus the aim is to reduce mortality and morbidity, prevent flares and avoid side effects. In serious cases of lupus nephritis (class III and IV), corticosteroids and immune suppres-sants (intravenous cyclophosphamide or mycophenolate mofetil) are used; they are effective in 55% of patients. Over the last few years, the doses of cyclophosphamide prescribed have been lowered without any effect on mortality

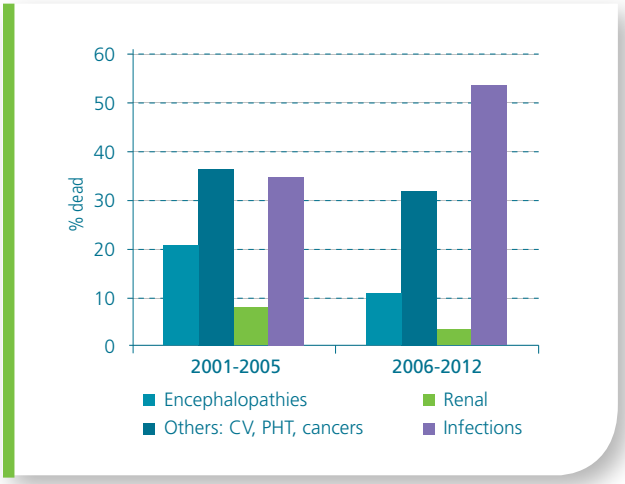
(10% mortality at one year); this has also reduced the side effects associated with this drug (osteonecrosis of the femoral head, osteoporotic vertebral compression, infections, ovarian failure). Mycophenolate mofetil has fewer side effects than cyclophosphamide and has the advantage of being administered orally. Corticosteroid/cyclophosphamide or corticosteroid/mycophenolate mofetil combinations are indicated as a first-line treatment, to induce a remission. Corticosteroids and Azathioprine© (or mycophenolate mofetil) are then prescribed, as a maintenance therapy, to prevent relapses.

Other treatment strategies will soon be available, aimed at the molecular targets underlying the disease. Two are already on the market: Rituximab© (anti-CD20 antibody) and Belimumab© (anti-BLyS antibody). Belimumab has a marketing authorisation for cutaneous and articular lupus; Rituximab does not have a marketing authorisation, but can be administered under an «ATU» (pre-market authorisation for compassionate use) for very severe forms. Other biotherapies are expected in the near future, in particular an anti-CD40 antibody and Abatacept© (CTLA4-Ig).

Mortality

Mortality in patients with a severe form of lupus has fallen in recent decades: before 1955, the 5-year survival rate was below 50%, but now 10-year survival is in excess of 90% and 15-year survival has reached approximately 80%.

Causes of deaths over the last two decades % of deaths



Source : Fei Y et al. Clin Rheumatol 2013

A graduated, adapted therapeutic response

Biotherapies	Severe forms only
Corticosteroids	Visceral forms
Immune suppressants	
NSAIDs – hydroxychloroquine	Minor forms
Analgesics	
No treatment or symptomatic treatments	

Nevertheless, the lupus-related death rate remains 2.4 times higher than in the general population.

The less serious cutaneous, articular and visceral forms in the main do not have any repercussions on the death rate. However, they can be very incapacitating. The causes of early death from lupus are often connected to severe forms of the disease: lupus nephritis, brain involvement, cardiovascular involvement and infections to which patients can become more susceptible due to their treatment, in particular immune suppressants. Lupus nephritis, however, is no longer a major cause of death: it has fallen considerably over the years. Cardiovascular involvement related to atheroma causes later deaths, generally after the age of 35.

Class III and IV lupus nephritis are the most serious forms; if untreated, they can develop into end-stage kidney disease or nephrotic syndrome. About 50% of people with lupus have classic cardiovascular risk factors such as a sedentary lifestyle, hypercholesterolemia and obesity, to which the specific lupus-related risk factors are added: renal failure, chronic inflammation, accelerated oxidation of LDL molecules.

To sum up: the causes of early death are lupus nephritis (classes III, IV and VI), neuropsychiatric lupus, cardiovascular involvement (in particulars myocarditis), pulmonary involvement (embolism) and certain iatrogenic complications (infections). The secondary causes of death are related to the associated comorbidities; these can be numerous: hypertension, dyslipidemia, atherosclerosis, coronary heart disease, diabetes, bone disorders (osteoporosis, osteonecrosis), malignant conditions (non-Hodgkin's lymphoma, bronchial cancer and hepatobiliary cancer).

Points to remember for risk selection

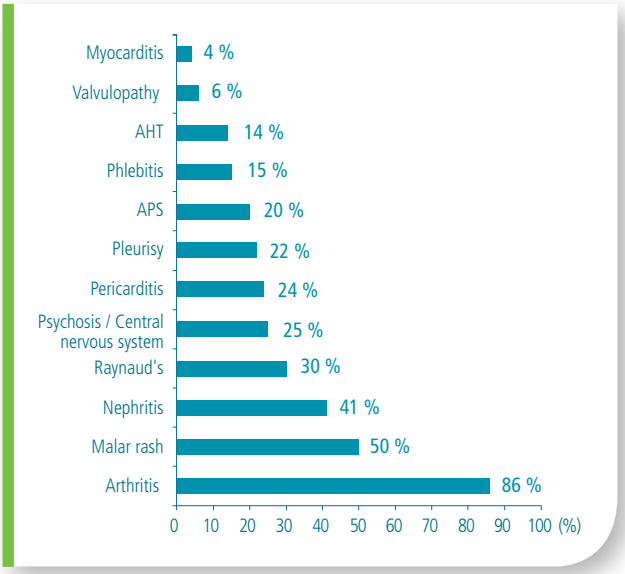
Average 10-year survival is now more than 90% and 15-year survival has reached approximately 80%.

Lupus is a polymorphous disease: a distinction should be made between the serious forms (lupus nephritis, neuropsychiatric lupus, infections, cardiac involvement), which are causes of early death, and moderate forms (cutaneous, articular), which can nevertheless lead to frequent periods off work. Cardiovascular conditions and cancer are later complications of lupus. Antiphospholipid syndrome (APS), frequently associated with the disease, is also an aggravating factor (arterial and venous thrombosis, pulmonary embolism).

Pregnancy, a high-risk period for both mother and child, can be envisaged if the lupus has been in remission for preferably two years, but as a minimum at least twelve months (no lupus nephritis, central nervous system lupus or cardiac flares during the period). For the mother, the greatest risk is around the 3rd trimester and post-partum, with the possible occurrence of complications: lupus flare, pre-eclampsia, venous or arterial thrombosis: For the child, the risks vary: foetal death in utero, premature birth, miscarriage, hypotrophy, neonatal lupus. Pregnancy must therefore be planned and appropriate treatments given.

The assessment of the disease activity and the risks involves **analysing different elements in the patients' medical file:** a recent (in the last 6 months) specialist follow-up assessment, possible hospital reports, biological tests (CBC, platelets, ESR, CRP). The markers for disease activity will be the complement C3 level (a low C3 level can herald a lupus flare) and antibodies to native DNA as well as creatinemia, proteinuria and haematuria for kidney function.

Main clinical signs in 435 lupus sufferers



Source : Hôpital La Pitié Salpêtrière, Paris, France

Major features of Lupus:

Its rarity: prevalence estimated at 15 to 50 per 100 000.

Its occurrence: it occurs predominantly in women of child-bearing age (9 times out of 10).

Its clinical expression: extremely polymorphous, ranging from quite benign cutaneous and articular forms to serious forms with organ involvement, including the kidneys and the CNS.

Its diagnosis: requires a combination of clinical and/or biological symptoms, in particular the presence of antinuclear antibodies, and more particularly antibodies to native DNA.

Its course: in flares, sometimes triggered by identifiable environmental factors.

Its prognosis: dominated by three types of complications: renal, neurological and cardiovascular, currently with a 10-years survival average of about 90%.

A guarded approach for:

The first few years • Complications: visceral, renal, neuropsychiatric, cardiovascular and infections • Depending on the cover sought, the risks and the form of the disease (minor, moderate, severe).