

Lupus Erythematosus

What is lupus erythematosus?

Lupus erythematosus, commonly known as lupus, got its name from the distinctive facial rash that gives a patient the appearance of having been attacked by a wolf. The rash, which is also known as a butterfly rash, typically occurs after exposure to sunlight. This, however, is only one of the many different features of this autoimmune disease, which in the form of systemic lupus erythematosus (SLE) can affect almost every organ. Autoimmune diseases have in common to result from a failure in the immune system's ability to distinguish between an individual's own tissues and invading organisms such as bacteria and viruses. Of all of the autoimmune diseases, lupus is the classic example of a condition caused by autoantibodies.

Lupus erythematosus is a complex disease of the immune system. If it becomes systemic and is not treated properly, patients die. Over the last twenty years, medicines have been introduced which have helped people survive. Scientists are continuing to research the underlying mechanisms of this disease.



As part of an aberrant immune response, white blood cells – known as B lymphocytes – produce and release autoantibodies, i.e. abnormal antibodies that react against the body's own molecules, such as deoxyribonucleic acid (DNA) and particular proteins, contributing to inflammation and tissue damage. Binding of the autoantibodies to the body's components results in the formation of immune complexes and triggers a cascade of inflammatory processes. This includes the release of cytokines and the activation of the body's complement system, leading to the typical redness of the skin which is where the word *erythematosus* comes from.

Certain autoantibodies are found in the blood many years before a person is diagnosed with lupus, while others appear just before the onset of disease symptoms. The discovery of which autoantibodies arise first may offer new insights into the potential triggers of lupus.

Who does lupus erythematosus affect?

Lupus is relatively rare, affecting approximately 40 people per 100,000 population, of whom 95 per cent are women. This prevalence leads to an estimate of some 200,000 patients in Europe. More than 100 genes are thought to be involved in SLE. Because the precise genes involved may vary from population to population, it is not surprising that the incidence of SLE varies in the regions of the world.

Globally, lupus is more common in coloured people and Asians than in Caucasians. For Caucasian women between the ages of 15 and 64, the prevalence is one per 700 women. For African-American women of the same age group, the prevalence is one per 245 women. The disease is not contagious and can occur at any time of life, but typically starts between the age of 20 to 30 years. A family history plays a strong role in SLE; a sibling has 20 times the risk as someone without an immediate family member with the condition.

Present treatments:

Anti-inflammatory medications are the most commonly used medicines for lupus treatment, particularly for symptoms such as fever, arthritis (inflammation of the joints), or pleurisy (inflammation of the lining of the lung). In the majority of patients, anti-inflammatory molecules are the only medications that are ever required to control their condition. Anti-inflammatory medicines fall into two categories: non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

For unknown reasons, people often respond better to one NSAID than another. Thus, it may be necessary to treat a person with several different medications to determine the most effective one. Individuals with more severe or serious lupus symptoms, such as kidney disease, anaemia or low platelet counts may require corticosteroids, naturally occurring hormones with immunosuppressant and anti-inflammatory properties. Furthermore, anti-malaria medicines are widely used in the management of lupus symptoms. They are particularly effective in the treatment of arthritis, skin rashes, or mouth ulcers.

Immunosuppressive or cytotoxic compounds are generally reserved for patients with more serious manifestations of lupus, such as nephritis or neurological disease, in whom treatment with corticosteroids has failed. The compounds have a major effect on cells produced by the bone marrow, including white blood cells, red blood cells, and platelets. Individuals treated with immunosuppressants or cytotoxic medications must be very carefully monitored to avoid low counts of red and white blood cells and the development of serious viral infections.

If not treated properly, SLE is fatal. Achievements in treatment during the last two decades have resulted in a reduction in mortality in lupus patients with 10-year survival rates ranging from 75 to 85 per cent, with more than 90 per cent of patients surviving more than 5 years.

What's in the development pipeline?

A number of investigational medicines for lupus are currently being studied in clinical trials. New treatments to improve lupus symptoms and reduce the need for corticosteroids include hormone modifications, such as blocking the secretion of the hormone prolactin with bromocriptine, more selective immunosuppressive compounds and biological agents. Biologicals, such as human monoclonal antibodies and immune response modifiers, are being used to selectively block the forming of autoantibodies or the activation of the inflammatory process – both new and exciting approaches for therapy and prevention of the disease. The main candidates where SLE is the primary indication are a B lymphocyte activating factor inhibitor, and an immuno-conjugate, both in Phase 2 clinical trials.

A medicine approved for the prevention of organ rejection in transplant patients may provide an alternative to current treatment options for patients with lupus nephritis. Phase 3 clinical studies are underway with the aim of obtaining its approval in this indication.

The investigational medicine dehydroepiandrosterone (DHEA) is being studied in several Phase 3 clinical studies to alleviate symptoms and reduce reliance on the standard steroid therapy. The mode of action is its conversion to potent androgenic steroidal compounds. The interest in DHEA as a therapeutic intervention in lupus stems from the high preponderance of females with the disease and the observation that estrogens may contribute to disease activity, whereas androgens may provide a protective effect.

The longer-term future:

Understanding the checks and balances of the body's built-in mechanisms to avoid autoantibody production is an active area of lupus research. Potential therapeutic targets include B lymphocytes, T lymphocytes, autoantibodies, circulating immune-complexes, cytokines, cytokine-receptors, complement proteins, and adhesion molecules.

Research has shown that abnormal production of interferon alpha (IFN-alpha) also plays a key role in the development of lupus. Apparently, material released by dying cells together with autoantibodies triggers the production of IFN-alpha by specific immune cells. Results from other research groups suggest that defects in the body's ability to eliminate cells that die as a result of a programmed cell death, known as apoptosis, may contribute to the development of lupus. If these cells are not properly eliminated, the remaining cellular debris may foster the synthesis of antinuclear autoantibodies that trigger IFN-alpha-production.

It has also been suggested that IFN-alpha affects the actions of another immune mediator, known as interleukin 10 (IL-10). Under most circumstances, IL-10 has anti-inflammatory effects, serving to contain tissue injury by limiting the duration and intensity of immune and inflammatory reactions. However, in some situations in which the immune system is overactive, IL-10 acquires inflammation-promoting activity. Investigations have shown that IFN-alpha can alter the balance between the pro-inflammatory and anti-inflammatory actions of IL-10, tipping the scale in chronic auto-immune or inflammatory diseases towards inflammation. Interference with the formation and action of IFN-alpha-producing triggers is one strategy for new, more targeted therapies.

A naturally occurring protein may be able to reverse chronic kidney damage in lupus patients. The compound, called bone morphogenetic protein 7 (BMP-7), is known to stimulate bone formation. Researchers found that BMP-7 reverses a process that generates scar tissue, known as fibrosis. Fibrosis plays a major role in the development of end-stage kidney failure in lupus. If future studies show that BMP-7 works in humans, the protein could be used to reverse chronic kidney damage, reduce the need for dialysis, and improve patients' quality of life.



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