



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

LUPUS: AN OVERVIEW

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with an annual incidence of 50 to 70/million and a prevalence of 500/million population. The highest incidence is observed in women aged 20 to 40 years. The clinical manifestations of SLE are remarkably heterogeneous. Major organ system involvement may occur in the heart, lungs, kidneys, and central nervous system and is responsible for most of the mortality and morbidity caused by the disease. Complications of drug treatment, in particular corticosteroid side effects, contribute to long-term morbidity. The major causes of death are directly related to the disease and include acute vascular neurologic events, renal failure, cardiovascular or pulmonary involvement, infection, and coronary artery disease.

NEW TREATMENTS

Researchers continue to look for more effective lupus treatments. Some studies have focused on blocking the expression of genes that may cause some of the symptoms of lupus, but any drugs that might result from this research are still years away.

Scientists are also investigating the use of existing drugs to treat lupus. One medication that has received attention is the cancer drug rituximab (Rituxan), which works by lowering the number of white blood cells in the body. Although people with lupus usually have lower than normal B cell counts, the B cells that do exist are involved in the autoimmune process. Studies of people with lupus who were treated with rituximab have shown promise, though more study is needed.

In late 2006 the U.S. Food and Drug Administration (FDA) issued a warning to doctors advising them to use caution in prescribing rituximab to people with SLE. Two people with SLE who took rituximab died after contracting a serious brain infection. Though rituximab isn't approved for use in people with lupus, doctors can prescribe the drug for this use if they feel it may help.

CURRENT TREATMENT OPTIONS

Nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin or other NSAIDs such as naproxen sodium and ibuprofen may reduce joint pain and inflammation.

Antimalarial drugs. Although there's no known relationship between lupus and malaria, these medications may be useful for treating skin and joint problems and the ulcers that some people develop in the mouth or nose. Antimalarials may also prevent flares of the disease. Hydroxychloroquine (Plaquenil), the most commonly prescribed antimalarial, is sometimes used to control lupus in pregnant women because it appears to have fewer risks to the fetus than other medications used to treat lupus do.

Corticosteroids. These drugs counter the inflammation of lupus, but can have serious long-term side effects, including weight gain, easy bruising, thinning bones (osteoporosis), high blood pressure, diabetes and increased risk of infection, already a major concern for people with lupus. The risk of side effects increases with higher doses and longer-term therapy. Corticosteroids are sometimes combined with another medication to help reduce the dose, and therefore the toxicity, of both drugs.

Immunosuppressive medications. Drugs such as azathioprine (Imuran) and cyclophosphamide (Cytoxan) work by suppressing the immune system. Other medications that may be used to treat lupus include methotrexate (Rheumatrex), chlorambucil (Leukeran), cyclosporine (Neoral, Sandimmune) and mycophenolate mofetil (CellCept). Because immunosuppressive medications can have serious side effects, they're usually reserved for people with severe systemic disease or organ failure. Immunosuppressive drugs can cause anemia and a low white blood cell count, and increase the risk of infection and cancer.

CURRENT (INDUSTRY-SPONSORED) PRODUCTS IN DEVELOPMENT

Product	Sponsor
Rituximab	Genentech
Abatacept	Bristol-Myers Squibb
Enteric-coated Mycophenolate Sodium	Novartis
Belimumab	Human Genome Sciences + GSK
CellCept plus Corticosteroids	Hoffmann-La Roche
MEDI-545	MedImmune, Inc.
Abetimus Sodium	La Jolla Pharmaceutical Company
Epratuzumab	Immunomedics

**RECENT ONGOING AND COMPLETED INDUSTRY-
SPONSORED PHASE II/III LUPUS STUDIES**

<i>Trial</i>	<i>Diagnosis</i>	<i>Sites</i>	<i>Patients</i>	<i>Enrollment Rates (pts/site/month)</i>
1	Moderate to Severe Systemic Lupus Erythematosus	55	250	~0.33
2	Systemic Lupus Erythematosus	101	300	~0.21
3	Systemic Lupus Erythematosus (completed)	57	180	~0.18
4	Systemic Lupus Erythematosus	82	810	~0.65
5	Systemic Lupus Erythematosus	100	300	~0.25
6	Class III or IV Lupus Nephritis	62	140	~0.20