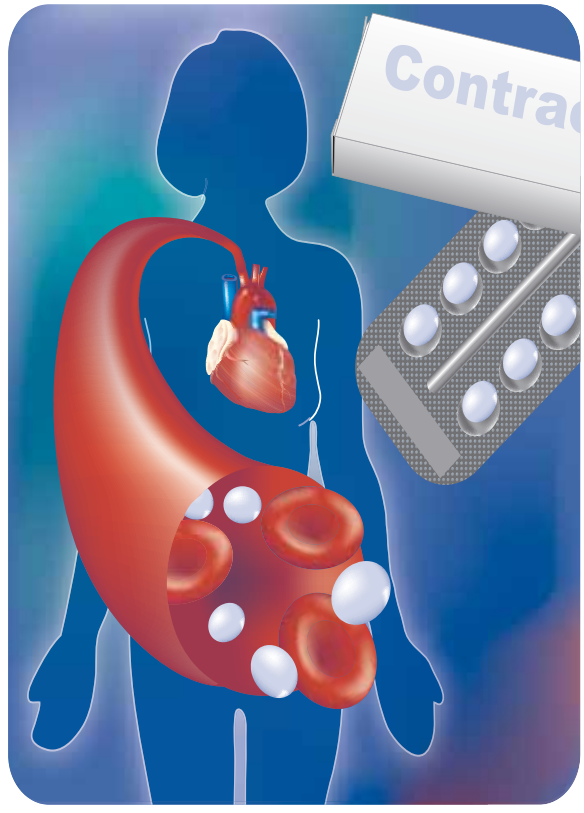
Good news for lupus sufferers as two studies show that they may take oral contraceptives containing estrogen without increased risk of disease flares

Oral contraceptives safe for lupus patients

Two separate studies published in the *New England Journal of Medicine* have shown that women with systemic lupus erythematosus (SLE) can take oral contraceptives safely. This is in contrast to past medical advice that has held exogenous estrogen to be harmful and lead to disease flares in these patients. The results have many positive implications for women of childbearing age suffering from SLE.

The Lupus Foundation of America estimates that approximately 1.5 million Americans have a form of lupus. SLE is a chronic autoimmune disease affecting joints, muscle, skin, blood and sometimes organs, including the kidney, heart and brain. The disease is nine-times more common in women than in men, leading people to believe that hormones may play a major role. This was also supported by the fact that women typically develop lupus during their childbearing years, when female hormone levels are at their peak.

Previous studies showed that in both human patients and mouse models of lupus, administration of hormonal contraceptives led to disease worsening and flares. However, according to Michelle Petri from Johns Hopkins University School of Medicine, MD, USA, the oral contraceptives used in the previous trials contain more estrogen than those used today. Bonnie Bermas from the Brigham and Women's Hopsital, MA, USA, who wrote an editorial to accompany the latest studies, also notes that a previous study enrolled patients with active nephritis, whereas all patients taking part in the more recent trials had stable, mild or inactive disease activity.



Petri and colleagues conducted a double-blind, randomized, noninferiority trial, involving 183 women with SLE at 15 centers in the USA. The patients were randomly assigned to either oral contraceptive or placebo groups (containing 91 and 92 women, respectively) and evaluated at 1, 2, 3, 6, 9 and 12 months. Severe flares occurred in 7 of the 91 subjects receiving oral contraceptives and 7 of the 92 in the placebo group. The number of mild-to-moderate flares was also similar between the two groups (1.40 flares per person-year in the contraceptive group vs 1.44 flares per person-year in the placebo group), giving a relative risk of 0.98. The study concluded that: "oral contraceptives do not increase the risk of flare among women with SLE whose disease is stable".

A second study, conducted by Jorge Sanchez-Guerrero of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, and colleagues, found similar results. Here, 162 women were administered with either oral contraceptives containing estrogen, nonestrogen oral contraceptives or intrauterine devices. Participants were assessed at 0, 1, 2, 3, 6, 9 and 12 months using the SLE disease activity index. Results showed all demographic features and disease activity (including flares) to be similar in the three groups. The researchers found: "there were no significant differences among the groups...in global, maximum disease activity, incidence or probability of flares or medication use".

'...oral contraceptives do not increase the risk of flare among women with SLE...'

Not only have these results "shaken up the whole notion of what's contributing to lupus" (Petri), there are also a number of benefits for female SLE sufferers in being able to take oral contraceptives. The reluctance of doctors to prescribe estrogen to women patients has meant that other, less effective contraceptives have been used; however, some lupus medications can be harmful to fetuses. Planned conception and pregnancies are also desirable, as pregnancies during remission have better outcomes. Oral contraceptives may help to maintain ovarian function, thereby mitigating infertility; they may also reduce loss of bone density, which can lead to osteoporosis; both infertility and osteoporosis can result as side effects of lupus treatments.

Priority Paper Alerts

Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis.

O'Dell JR, Petersen K, Leff R *et al.*: *J. Rheumatol.* [Epub ahead of print] (2005).

This study aimed to determine the efficacy and safety of etanercept when combined with sulfasalazine (SSZ), hydroxychloroquine (HCQ) and gold for treating rheumatoid arthritis (RA). 119 patients with active disease, despite stable therapy with HCQ, SSZ or intramuscular gold, were enrolled. American College of Rheumatology scores were evaluated at 24 and 48 weeks as the primary end point. Patients in all etanercept combinations showed significant improvement. Etanercept was shown to be efficacious and well tolerated when used in combination with SSZ, HCQ and gold.

The effect of raloxifene following discontinuation of long-term alendronate treatment of postmenopausal osteoporosis.

Michalska D, Stepan JJ, Basson BR, Pavo I: *J. Clin. Endocrinol. Metab.* [Epub ahead of print] (2005).

This study compared bone mineral density (BMD) and biochemical markers of bone turnover in patients who had undergone long-term alendronate therapy. Women with postmenopausal osteoporosis who had taken alendronate (10 mg/day) for a mean period of 43 months were randomly assigned to receive raloxifene (60 mg/day), placebo or to continue with alendronate for 12 months. BMD and various biochemical markers were measured at baseline and follow-up visits. Continuation of alendronate gave the most pronounced BMD preservation and increase. Raloxifene showed beneficial effects on BMD and bone turnover compared with placebo.

Indications for plasma exchange in systemic lupus erythematosus in 2005.

Pagnoux C, Korach JM, Guillevin L: *Lupus* 14(11), 871–877 (2005).

Plasma exchange can be used for patients with SLE to remove autoantibodies and immune complexes from the blood. Efficacy has only been supported by noncontrolled and/or retrospective studies. This article reviews the main historical steps in the use of plasma exchange to treat SLE. Plasma exchange may be particularly beneficial for certain conditions, including refractory SLE renal disease, neuropsychiatric SLE, thrombotic thrombocytopenic purpura and catastrophic antiphospholipid syndrome. Today, few SLE patients undergo plasma exchange, although adverse events are rare. Recent advances in plasma exchange technologies may lead to their more widespread use in the therapeutic arsenal for SLE.

US$100 million definitive study into anti-inflammatories and heart disease

Pfizer funds a 20,000-patient study into anti-inflammatories and cardiovascular and gastrointestinal risk

A definitive study of anti inflammatories in heart disease is due to begin this year. Recently, there has been much controversy over the use of cyclooxygenase (COX)-2 inhibitors and nonsteroidal anti-inflammatories used to treat arthritis. It is hoped that this large, 20,000-patient study will provide some answers regarding which treatments are safe for arthritis patients to use.

The trial, known as the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), will compare celecoxib (a COX-2 inhibitor, manufactured by Pfizer as Celebrex) with naproxen and ibuprofen, traditional nonsteroidal anti-inflammatory drugs. Celecoxib is generally considered to be less harmful to the gastrointestinal tract, naproxen to give less risk of cardiovascular complications and ibuprofen to come somewhere between the two. All participants will be high-risk, secondary prevention patients with both arthritis and heart disease – this will be the first study to look specifically at these patients. All patients will also receive low-dose aspirin (against cardiovascular prophylaxis) and a proton pump inhibitor (as gastrointestinal tract protection) to ensure blinding across all three arms. The principal investigator of the study, Steven Nissen of the Cleveland Clinic, OH, USA, hopes that results will "sort out the cardiovascular safety, the gastrointestinal safety and also the pain relief" aspect of these drugs. This would benefit both patients and physicians, who sometimes struggle to advise patients as to the optimal treatment strategy.

PRECISION has estimated costs of approximately US$100 million, to be funded by Pfizer. The study has taken months to plan, a process that has involved both the US FDA and the European Medicines Evaluation Agency. Nissen has assured that "we are committed to…a high degree of independence". None of the investigators involved may have any financial relationship with any manufacturer of analgesics or anti-inflammatories, whether marketed or in development.

> 'All participants will be high-risk, secondary prevention patients with both arthritis and heart disease.'

Results will be available in 2010, although if there are major differences between the drugs, these may become apparent earlier. Business experts (and some cynics) have described this trial as a fair bet for Pfizer. If results show Celebrex to be the better drug, then sales could reach well into the billions. At the very least, the trial gives the company time to keep selling the drug, until the results are published.

Given the present climate of controversy and lawsuits surrounding the class of COX-2 inhibitors, clarity would be greatly welcomed by all those involved in the treatment of arthritis.

Abatacept approved for treatment of rheumatoid arthritis in the USA

Abatacept, a new anti-rheumatic biologic has been fast-tracked and is now approved by the US FDA. Abatacept, marketed as Orencia® and produced by Bristol-Myers Squibb, NY, USA, is the first drug in its class of costimulatory blockers and is indicated for treatment of rheumatoid arthritis (RA).

RA affects approximately 1% of the world's population. Many patients suffering from RA have benefited from the advent of tumor necrosis factor (TNF) blockers. However, there remains a significant minority of patients who do not respond adequately to previously available disease-modifying agents, such as TNF inhibitors and methotrexate. The novel mechanism of abatacept is its action as a selective modulator of the costimulatory signal required for full T-cell activation. It is hoped that this will translate into benefits for this minority of inadequate responders.

Two pivotal Phase III efficacy trials, the Abatacept Trial in Treatment of Anti-TNF INadequate responders (ATTAIN) and the Abatacept in Inadequate responders to Methotrexate (AIM) trials, both showed significant improvements in physical function and health-related quality of life compared with placebo.

The most serious adverse reactions against abatacept as compared with placebo were infections (3 vs 1.9%, respectively) and malignancies (1.3 vs 1.1%, respectively). No new side effects were shown during the trials, the most common being headache, nausea, nasopharyngitis and upper respitory tract infection. As with any drug that acts on the immune system, vigilance will be required regarding infections, as the drug is available to more patients. Abatacept is not recommended in combination with other biologic disease-modifying agents or for use by those with a history of infections.

In anticipation of increased production, Bristol-Myers Squibb has recently submitted a supplemental Biologics License Application to the US FDA for licensure of a third-party manufacturing facility. Analysts are forecasting abatacept to be the next 'blockbuster'. However, some physicians are more cautious, citing the fact that it must be administered intravenously as a potential drawback for some patients.

Smoking, genes and rheumatoid arthritis

Researchers in Sweden find the presence of anticitrulline antibodies to be of critical importance when evaluating the genetic and environmental risk factors for rheumatoid arthritis

Despite being one of the most common autoimmune diseases, RA still remains a mystery in many ways. Smoking is a known environmental risk factor and *HLA-DR* shared epitope genes are a recognized genetic risk factor for RA. A study published recently has shed light on the interaction between these two factors, finding that citrullinated peptides are important for determining the increased chances of developing the disease. This may well lead to further discoveries regarding the molecular mechanisms involved.

A Swedish team, led by Lars Klareskog of the Karolinska Institute, Stockholm, Sweden, focussed on citrulline-modified proteins, found in approximately two-thirds of RA patients. Smoking increased the chance of developing RA only in those patients who tested positive for anti-citrulline antibodies. Similarly, single or double copies of *HLA-DR* also increased the risk factor in these individuals only. In people who test positive for anti-cirulline antibodies who also smoke and carry two copies of the *HLA-DR* shared epitope genes, the relative risk of developing RA is increased 21-times.

Hopefully, this will lead to new understanding of the disease process and allow new opportunities to interfere with RA-inducing events before the onset of clinical symptoms.

Bextra not allowed back onto the Canadian market

Bextra (valdecoxib), withdrawn voluntarily in April 2005, will not be allowed back onto the market in Canada following a review of safety information by Health Canada. The selective COX-2 inhibitor was suspended owing to safety concerns regarding rare, serious skin reactions and cardiovascular problems.

This decision has been based on information from, and communications with, the manufacturer, external experts and the public as part of the COX-2 Expert Advisory Panel. This was initiated following the voluntary withdrawal or Vioxx® (rofecoxib) from the market in 2004. The conclusion was that there is insufficient evidence to establish the safety of the drug under its current conditions of use.

Celecoxib (Celebrex, Pfizer) is now the only COX-2 inhibitor available in Canada and the USA. In many European and Latin American countries, etoricoxib (Arcoxia, Merck & Co.) and parecoxib (Dynastat, Pfizer) are still on the market.

The advisory panel also concluded that: "available evidence indicates that COX-2 inhibitors and all other nonsteroidal anti-inflammatory drugs are associated with an increased risk of cardiovascular events. However, the exact nature of that increased risk may differ from one product to another".