Chloroquine May Lower Heart Disease Risk in RA

Rheumatoid arthritis patients on chloroquine have lower levels of antibodies to oxidized LDL.

BY KERRI WACHTER
Senior Writer

BUDAPEST, HUNGARY — Chloroquine therapy for patients with rheumatoid arthritis may lower levels of antibodies to oxidized low-density lipoprotein, and thus reduce the risk of cardiovascular disease, C.L.P. Mangueira, M.D., reported at the 4th International Congress on Autoimmunity.

Oxidized low-density lipoprotein (oxLDL) induces antibody production and the inflammatory process.

These antibodies (anti-oxLDL) are also considered risk factors for cardiovascular disease.

In a study of 66 rheumatoid arthritis (RA) patients and 66 age-matched healthy controls, "we found an apparent association between the use of chloroquine and low levels of the antibodies to oxidized LDL," said Dr. Mangueira of Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

This association is compelling because almost 50% of deaths among RA patients are due to cardiovascular causes and the onset of heart disease in RA patients has also been shown to start a decade earlier compared with those without RA.

The researchers evaluated the levels of anti-oxLDL by two different methods and compared them with those of the controls.

Anti-oxLDL was measured by an immunoassay that uses copper-oxidized LDL as antigen and another immunoassay that uses synthetic peptides derived from the fragmentation of apolipoprotein B as antigen. Both assays were developed by Dr. Mangueira's group.

RA patients were using methotrexate, prednisone, sulfasalazine, chloroquine, and leflunomide.

"We found higher levels of anti-oxLDL in rheumatoid patients compared with the control group," using both methods, Dr. Mangueira said. There was no statistical correlation between anti-oxLDL levels and disease severity, which was assessed using the Modified Disease Activity Score system, the erythrocyte sedimentation rate, and C-reactive protein.

The 22 chloroquine patients had lower levels of anti-ox-LDL than did RA patients with no chloroquine use. In addition, the RA patients taking chloroquine had lower levels of anti-apolipoprotein B peptides than did those not taking the drug.

"We know that chloroquine has a cholesterol-lowering effect," he said. In fact, chloroquine use has been suggested to reduce lipoprotein synthesis induced by corticosteroids in rheumatoid and lupus patients. ■

Anti-TNF Agents Are Proving Safe, Effective in Everyday Practice Settings

BY BRUCE JANCIN
Denver Bureau

BERLIN — Studies of anti–tumor necrosis factor therapy for rheumatoid arthritis are growing in size and enrolling more "real world" patient populations, compared with the earlier pivotal trials that won marketing approval for the biologic agents.

Results of two such studies presented at the annual European Congress of Rheumatology reaffirm the safety and efficacy of adalimumab and infliximab; earlier trials for these drugs had been criticized for their highly restrictive eligibility requirements and unrepresentative patient populations.

The biggest of these "real life" trials, which are intended to more accurately mirror clinical practice, is the ongoing Research in Active Rheumatoid Arthritis (ReAct) trial, an open-label study that to date has enrolled 6,500 patients at more than 430 sites in 11 European countries.

Participants in ReAct have longstanding moderate to severe rheumatoid arthritis (RA) of a mean 11 years' duration that has responded inadequately to at least one traditional disease-modifying antirheumatic drug (DMARD). Comorbid illnesses—commonplace among patients with RA—are no exclusion to participation in ReAct. Patients received 40 mg of adalimumab subcutaneously every other week in addition to any preexisting but inadequate therapy, most often methotrexate.

Gerd R. Burmester, M.D., presented data on treatment efficacy and safety at week 12 in the first 2,008 participants in ReAct, sponsored by Abbott Laboratories.

Median tender joint count fell from a baseline of 13 to 3. The swollen joint count dropped from 10 to 3. Clinical remission at 12 weeks, as defined by a Disease Activity Score–28 of less than 2.6, was achieved by 24% of patients; mean baseline DAS-28 was 6.0. Similarly, from a mean baseline Health Assessment Questionnaire score of 1.6, 25% of patients dropped below 0.5, a rate indicative of normal physical functioning.

Two-thirds of patients who achieved an ACR 20 by 12 weeks did so within 2 weeks of their first dose.

DR. BURMESTER

Also at 12 weeks, 67% of patients obtained at least a 20% reduction in disease signs and symptoms, or ACR 20. Adalimumab's onset of action was swift: Two-thirds of patients who achieved an ACR 20 by 12 weeks did so within 2 weeks of their first dose, reported Dr. Burmester, at Humboldt University, Berlin.

Of particular clinical interest was the efficacy of adalimumab in patients, regardless of whether they had previously failed therapy with other biologic agents. (See chart.) Also, efficacy was quite similar regardless of how many concomitant DMARDs patients were taking.

The 4.9% rate of serious infections in ReAct was similar to that of pivotal trials. "There were no new alerting signals," he said. Seven cases of tuberculosis occurred during 2,259 patient-years of follow-up.

In a separate presentation, Rene Westhovens, M.D., reported on 1,084 participants in the Safety and Efficacy of Infliximab Therapy in Rheumatoid Arthritis (START) trial. START was a multicenter study designed specifically to assess the infection risk associated with combined infliximab-methotrexate therapy in everyday practice and included 15 patients with previous active TB and another 45 with latent TB.

All participants were on methotrexate, and they were randomized to the standard 3 mg/kg of IV infliximab at weeks 0, 2, and 6, and every 8 weeks thereafter for 22 weeks, or to 10 mg/kg of the TNF antagonist, or to placebo.

The rate of serious infections—defined as those resulting in death, hospitalization, or threat to life—was 1.7% among patients on placebo, 1.7% in those on standard-dose infliximab, and 5.3% in those on 10 mg/kg of infliximab. The adjusted relative risk of serious infection was 3.3-fold greater in patients on high-dose infliximab, said Dr. Westhovens of the Catholic University of Leuven (Belgium).

None of the patients with latent TB or prior active TB developed a relapse or flare of active TB during the Schering-Plough–sponsored study, he added. ■

ReAct Results: Adalimumab at 12 weeks

Target Outcome	Total Study Population 2,008	Prior Biologic Therapy 164	No Prior Biologic Therapy 708
ACR 20	67%	59%	67%
ACR 50	39%	32%	35%
ACR 70	17%	12%	14%

Note: Information on prior therapy was available for only 872 patients.
Source: Dr. Burmester

Lack of Infections Halts Etanercept Safety Trial

BY TIMOTHY F. KIRN
Sacramento Bureau

SAN ANTONIO — A clinical trial undertaken to evaluate etanercept tolerance by rheumatoid arthritis patients with comorbid conditions was stopped early because there were too few adverse events and infections to analyze, Scott W. Baumgartner, M.D., said at the annual meeting of the American College of Rheumatology.

The purpose of the study was to determine whether etanercept (Enbrel) use in patients with conditions such as diabetes might make them more prone to infections than has been suggested with initial trials of anti–tumor necrosis factor therapy, said Dr. Baumgartner, a private-practice researcher in Spokane, Wash.

The double-blind, placebo-controlled trial was to enroll 1,000 individuals, including 200 with diabetes, who would be treated and followed for 20 weeks each. After 535 patients were enrolled and treated, however, the data-monitoring safety board halted the trial, mainly because the infection rate was similar in both groups and the board believed that this result was unlikely to change.

At the same time, the trial researchers were having trouble recruiting subjects, since some people were reluctant to be assigned to placebo. Amgen Inc., the study sponsor, conferred with the Food and Drug Administration before canceling the study.

The majority of subjects in the study had either chronic obstructive pulmonary disease (42%) or diabetes (40%).

More subjects on placebo discontinued than did those on etanercept: 53 of 269 subjects compared with 29 of 266 subjects, respectively. The incidence of patients withdrawing specifically because of adverse events was 6% for placebo and 5% for etanercept.

The incidence of medically important infections in the study was 3.7% for placebo and 3.4% for etanercept. "And the types of infections seen were pretty similar, a few more [urinary tract infections] in the etanercept group and a few more [upper respiratory infections] in the placebo group," Dr. Baumgartner said.

The deaths of four patients in the etanercept group and one patient in the placebo group appeared to be unrelated to the drug because the patients were very ill, Dr. Baumgartner said. Two patients died from coronary events, one from a subarachnoid hemorrhage, and one from respiratory failure. ■