

Antibodies May Underlie Lipid Profiles in SLE

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BOSTON — Heightened activity of anti-double-stranded DNA antibodies may contribute to the poor cholesterol profiles of patients with active systemic lupus erythematosus, according to study findings.

Patients with SLE are often afflicted with a complex triad of risk factors involving high levels of serum triglycerides,

high levels of VLDL cholesterol, and low levels of HDL cholesterol. These can hasten the development of premature atherosclerosis and coronary artery disease. Though researchers have posited several theories to explain this phenomenon, its etiology remains unknown.

Sara Kashef, M.D., and colleagues from the Shiraz University of Medical Sciences in Fars, Iran, compared serum lipoprotein levels and antibody activity in 30 patients with active lupus with that of 16 patients

with inactive lupus, and 41 healthy controls matched for age and sex. Lupus activity was measured using the SLE disease activity index (SLEDAI). Dr. Kashef presented the study in a poster session at the annual meeting of the Federation of Clinical Immunology Societies.

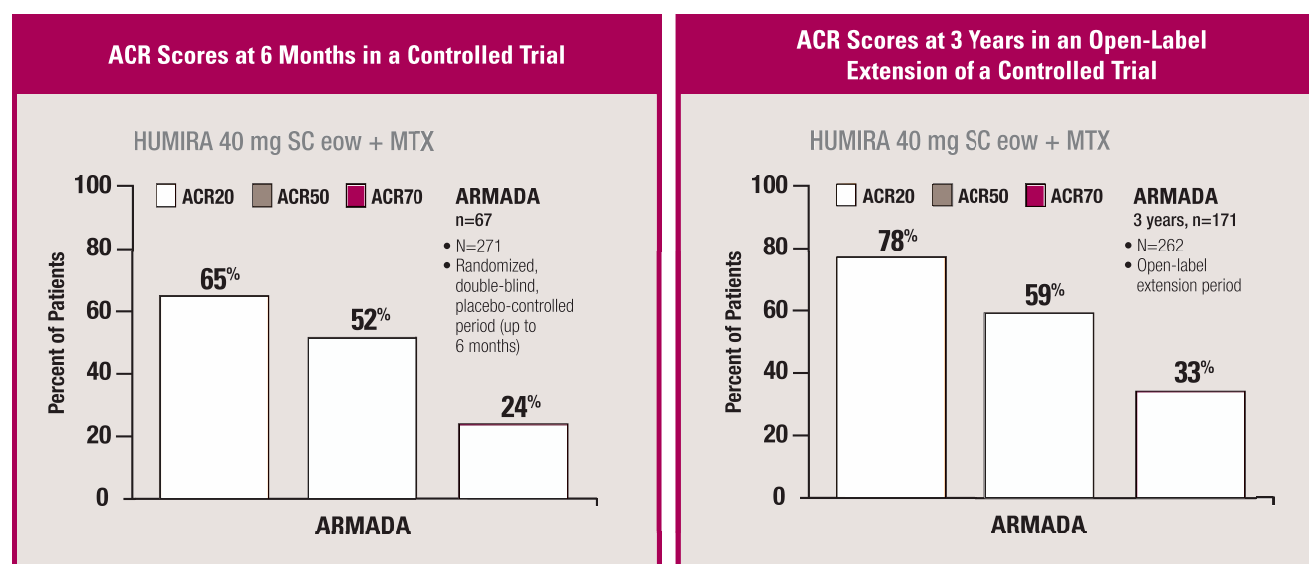
Compared with healthy controls and people with inactive SLE, patients with active SLE had significantly higher levels of triglycerides and VLDL cholesterol, and lower levels of HDL cholesterol.

Moreover, poor cholesterol profiles were significantly more likely to appear in patients who tested positive for anti-dsDNA antibodies than in those who tested negative. There was no correlation between dyslipoproteinemia and anticardiolipin antibody activity, another suspect in the genesis of SLE atherosclerosis.

“The appearance of this pattern of dyslipoproteinemia—high triglycerides and VLDL cholesterol and low HDL cholesterol—in this selected group of patients

IT'S ABOUT RESPONSE

ACR SCORES MAINTAINED IN MODERATE-TO-SEVERE RA²⁻⁴



The above analysis is the intent-to-treat study population using nonresponder imputation methodology. Patients who withdrew or had missing values were considered nonresponders.

The above analysis is as-observed at the indicated time points. Patients with missing data were excluded.

TRIALS DESIGNED TO MATCH REAL-LIFE PATIENTS^{1,3-6}

BASELINE PATIENT DEMOGRAPHICS IN HUMIRA TRIALS ARMADA + DE019^{1,3-6}

- All trial patients had inadequate response to MTX
- Failed up to 3 DMARDs
- Disease duration (years): 10.0 to 12.5
- Mean HAQ DI: 1.4 to 1.6
- Mean CRP (mg/dL): 1.6 to 3.1

IMPORTANT SAFETY INFORMATION

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. HUMIRA can be used alone or in combination with MTX or other DMARDs.

TUBERCULOSIS (TB) AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF-BLOCKING AGENTS, INCLUDING HUMIRA. PATIENTS SHOULD BE EVALUATED FOR LATENT (INACTIVE) TB WITH A SKIN TEST. TREATMENT OF TB SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. THE BENEFITS AND RISKS OF HUMIRA SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF TREATMENT FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TB OR HISTOPLASMOISIS IS ENDEMIC.

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF-BLOCKING AGENTS, INCLUDING HUMIRA. MANY OF THESE INFECTIONS OCCURRED IN PATIENTS PREDISPOSED TO INFECTIONS BECAUSE OF CONCOMITANT IMMUNOSUPPRESSIVE THERAPY IN ADDITION TO THEIR UNDERLYING DISEASE. PATIENTS WHO DEVELOP A NEW INFECTION WHILE USING HUMIRA SHOULD BE MONITORED CLOSELY. TREATMENT SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. DO NOT START HUMIRA IN PATIENTS WITH ACTIVE

INFECTION (INCLUDING CHRONIC OR LOCALIZED), OR ALLERGY TO HUMIRA OR ITS COMPONENTS. EXERCISE CAUTION IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR WITH UNDERLYING CONDITIONS, WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS.

The combination of HUMIRA and anakinra is not recommended. TNF-blocking agents, including HUMIRA, have been associated in rare cases with exacerbation of demyelinating disease. Exercise caution when considering HUMIRA for patients with these disorders. Lymphoma has been observed in patients treated with TNF-blocking agents. The role of TNF-blocking agents in the development of malignancy is not known.

Anaphylaxis has been reported rarely following HUMIRA administration. Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including HUMIRA, and new onset CHF has been reported with TNF-blocking agents.

Most frequent adverse events vs placebo from placebo-controlled studies were injection site reactions (20% vs 14%), upper respiratory infection (17% vs 13%), injection site pain (12% vs 12%), headache (12% vs 8%), rash (12% vs 6%), and sinusitis (11% vs 9%). Discontinuations due to adverse events were 7% for HUMIRA vs 4% for placebo.

seems to be a consequence of disease activity and SLE disease itself," according to the authors. "Titers of anti-dsDNA correlated significantly with increased SLEDAI scores and low HDL cholesterol," they noted.

Recent research suggests that the enzyme, lipoprotein lipase (LPL), may play a key role. LPL breaks down VLDL cholesterol. And when LPL is impaired, VLDL cholesterol proliferates, leading to an unhealthy duet of high triglycerides with low HDL choles-

terol, the investigators explained.

Although antibodies to LPL were not measured, previous research suggests that increases in such antibodies are common in SLE patients (Arthritis Rheum. 2002;46:2957-63).

"These results reflect that one of the contributory causes of dyslipoproteinemia in active SLE is probably increased cross-reactivity of anti-dsDNA antibodies with LPL due to high production of these antibodies in the active phase of disease,"

the investigators suggested.

Although these findings support an underlying autoimmune cause of dyslipoproteinemia in lupus patients with active disease, other factors likely contribute as well, the researchers said. These include inflammatory mediators (e.g., tumor necrosis factor, interleukin, interferon) that are known to suppress LPL activity and cause dyslipoproteinemia in SLE (Arthritis Rheum. 2003;48:2533-40), as well as physical inactivity. ■

VERBATIM

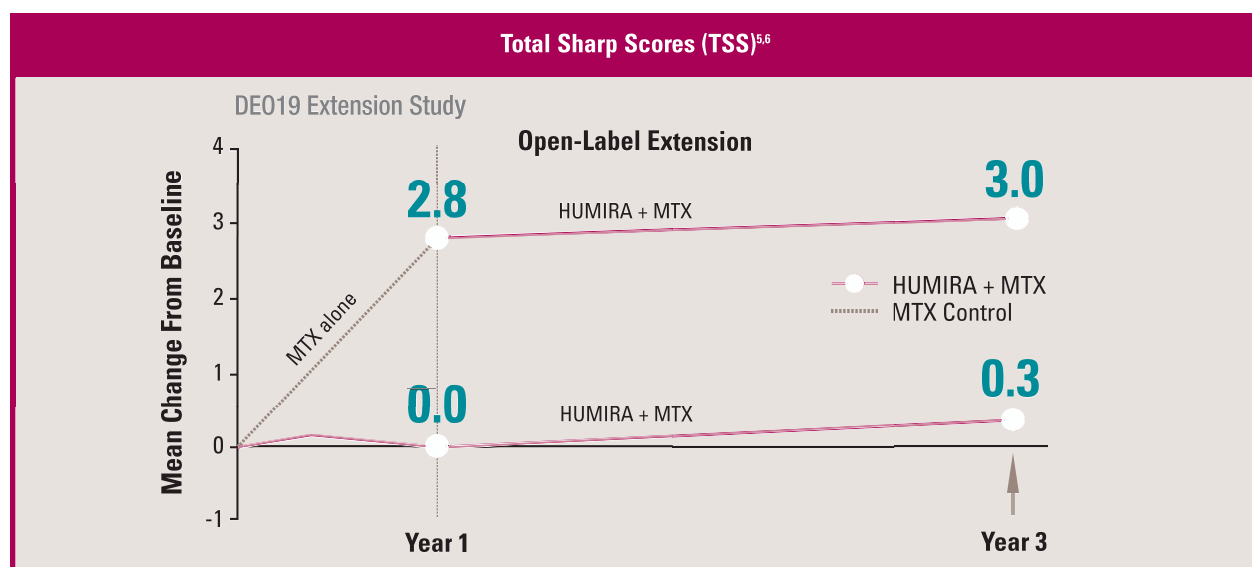
'To say that "you better meet every single one of these principles and guidelines," that's digging in your heels—and tying your hands.'

Dr. Mary Frank, president of the American Academy of Family Physicians, expressing doubt about the AMA's tactics on 'pay for performance,' p. 26

IT'S ABOUT

RADIOGRAPHIC EVIDENCE

INHIBITION OF DISEASE PROGRESSION IN MODERATE-TO-SEVERE RA^{5,6}



Year 1 and year 3 x-rays were assessed for changes from baseline in TSS.

Study DE019-619 patients entered a randomized, double-blind, placebo-controlled period up to 1 year. 457 patients entered the open-label extension period.

- In the DE019 extension study, a majority of patients continued to show *no radiographic progression* (≤ 0.5 -unit increase from baseline) at 3 years ($n=129$)⁶
 - 61% based on Total Sharp score (mean change=0.3)
 - 71% based on Joint Erosion score (mean change=0.1)
 - 73% based on Joint Space Narrowing score (mean change=0.2)

HUMIRA[®]
(adalimumab)

References: 1. Data on File. Abbott Laboratories. 2. HUMIRA full prescribing information. 3. Weinblatt ME, Keystone EC, Furst DE, et al. The ARMADA trial: sustained efficacy and long-term safety of adalimumab (HUMIRA[®]) plus methotrexate over 3 years in patients with long-standing rheumatoid arthritis. Presented at: European League Against Rheumatism Annual Scientific Meeting; June 2004; Berlin, Germany. 4. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. *Arthritis Rheum.* 2003;48:35-45. 5. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes

of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. *Arthritis Rheum.* 2004;50:1400-1411. 6. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic inhibition of structural damage sustained in patients with long-standing rheumatoid arthritis following 3 years of treatment with adalimumab (HUMIRA[®]) plus methotrexate. Presented at: American College of Rheumatology Annual Scientific Meeting; October 2004; San Antonio, Tex.

Please see brief summary of prescribing information on adjacent page.