

New Autoimmune Tx: Worms?

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ria also found in the gut performing important tasks such as producing vitamins and aiding in digestion, some helminths can cause disease in the host but many are harmless regulators of our immune systems.

At least one rheumatologist was skeptical. "This is an interesting theory—but just that."

"We need more documentation," said Dr. Roy D. Altman, professor of medicine, rheumatology, and immunology at the University of California, Los Angeles, in an interview. "In addition, longevity increases with the elimination of parasites. It may be that people are living longer and this allows them to get immune diseases like rheumatoid arthritis."

Dr. Weinstock is not advocating a return to 19th-century hygiene. Rather, he and other researchers are working to characterize more fully the interaction of helminths with the immune system and to identify factors responsible for the beneficial exposures so they can be reintroduced at an appropriate time early in life, when the immune system is developing. Clinical studies in IBD, asthma, rhinoconjunctivitis, and multiple sclerosis are underway and more are planned, and one helminth-de-

rived medication, ASP1002, is under review by the Food and Drug Administration and the European drug monitoring authorities.

Dr. Francois-Xavier Frapaise, CEO of Asphelia Pharmaceuticals Inc., confirmed his company is about to file an Investigational New Drug application for ASP1002 in Crohn's disease. They also are planning trials in conditions including lupus and multiple sclerosis. "RA would also be interesting to investigate," he said.

Dr. Weinstock noted: "Helminths exert a powerful effect on immunity in the host, primarily by inducing the regulatory arm of the immune system, which is important in reigning in the effector 'fight and kill' arm of the immune system." The regulatory arm hones and shapes the immune response to bacteria, viruses, and parasites, quelling the effects of the effector arm so as to prevent needless tissue damage.

Moreover, diseases such as asthma, IBD, RA, and multiple sclerosis remain uncommon in less-developed parts of the world where helminthic colonization is still widespread.

Initial animal experiments determined that helminth exposure could both prevent and reverse induced colitis in mice by in-

hibiting inflammatory cytokines such as tumor necrosis factor- α and interleukin (IL)-12 or by promoting the production of regulatory cytokines such as IL-10 and transforming growth factor- β (Int. J. Parasitol. 2007;37:457-64).

In a pilot study of 29 adult patients with longstanding, refractory Crohn's disease, patients were given a drink containing 2,500 specially prepared ova of *Trichuris suis*, the pig whipworm, every 3 weeks for 24 weeks. Ingestion of this helminth, which is similar to the human whipworm, colonized the human GI tract.

By the 12th week, 22 patients (76%) had responded, with a decrease in the Crohn's disease activity index (CDAI) of more than 100 points or below 150, and 19 patients (66%) were in remission, with a CDAI below 150. At the 24th week, 23 patients (79%) were responders and 21 (72%) were in remission (Gut 2005;54:87-90).

In a subsequent double-blind trial that enrolled 54 adult patients with ulcerative colitis, participants received 2,500 *T. suis* ova in a liquid drink or a placebo drink every 2 weeks for 12 weeks.

Favorable responses, with decreases in the ulcerative colitis disease activity index of 4 or more points on an index ranging from 0 to 12, were seen in 13 patients receiving the active treatment (43%) compared with 4 receiving placebo (17%).

Similar findings have been shown in several other autoimmune conditions. Prospective data have shown that children with helminths are less likely to develop allergies, and disease has been arrested in patients with multiple sclerosis following helminth colonization. Researchers in the United Kingdom have been investigating modulation of the immune system in rheumatoid arthritis. They tested an anti-inflammatory phosphorylcholine-containing glycoprotein secreted by the nematode *Acanthocheilonema viteae* in collagen-induced arthritic mice, finding a reduction in the severity of arthritis and suppression of collagen-specific T-1 cytokine production (Ann. Rheum. Dis. 2008;67:518-23).

Dr. Weinstock believes that helminths and human hosts evolved to the benefit of both over millennia. Petrified human stool many thousands of years old has been found to contain helminth eggs, and autopsies of mummies have found traces of helminths. The frozen iceman Ötzi, found in the northern Italian Alps in 1991 where he had lain buried in a glacier since 3300 B.C., had *T. trichiura* in his gut.

"We are teeming with life, and we really are part of the environment. When we try to separate ourselves from the environment and exposures to these organisms, we leave ourselves predisposed to disease," he said. ■

Systemic Sclerosis Has Unique Cardiac Risk

BY BRUCE JANCIN
Denver Bureau

PARIS — Periodic cardiac evaluations should be routine for all patients with systemic sclerosis, starting at "the first day of the disease."

Cardiac problems in patients with systemic sclerosis (SSc) were traditionally thought to occur mainly in those with the diffuse subtype of disease, not the limited cutaneous subtype. But with the use of contemporary cardiac evaluation tools, including tissue Doppler echocardiography, myocardial scintigraphy, and cardiac MRI, it has become apparent that coronary lesions occur very early in the course of both subtypes—and are far more prevalent than previously realized, Dr. André Kahan said at the annual European Congress of Rheumatology.

"I would say they are present in close to 100% of patients," said Dr. Kahan, professor of rheumatology at René Descartes University, Paris.

Subclinical myocardial perfusion abnormalities, diminished coronary reserve, and reduced left and/or right ventricular contractility are common in patients with SSc. The good news is that numerous studies by Dr. Kahan and others have demonstrated that these abnormalities are reversible with high-dose vasodilator therapy using calcium channel blockers or angiotensin-converting enzyme inhibitors. And bosentan has been shown to reverse the early abnormalities.

If the cardiovascular abnormalities aren't treated early, however, fibroblasts become activated, collagen is deposited, and irreversible myocardial fibrosis occurs.

When clinical cardiac disease is present, as in 15%-25% of SSc patients, all-cause mortality is sharply increased. Dr. Kahan cited one international study involving 3,311 SSc patients followed for nearly 20,000 person-years in which clinical cardiac involvement conferred



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DR. KAHAN

an adjusted 2.8-fold greater mortality (Am. J. Med. 2005;118:2-10).

The coronary disease present in SSc patients is completely different both in site and mechanism from that encountered in rheumatoid arthritis, systemic lupus erythematosus, or atherosclerotic heart disease in the general population. In those cohorts, the large coronary arteries are involved, while in SSc it is the small coronary vessels.

The vascular lesions in SSc patients are vasospasm-induced ischemic reperfusion injuries. Not just the small coronary arteries are affected, but small arteries everywhere else in the body, too, including the digits, pulmonary circula-

tion, and the kidneys. These vascular injuries and the resultant fibrotic changes lead to the major complications of SSc.

Tissue-Doppler echo is now widely available in routine cardiology practice; it provides an excellent noninvasive means of assessing left and right ventricular function. It is far more sensitive than standard echocardiography and should be applied routinely in all SSc patients, in Dr. Kahan's view.

Cardiac MRI is probably the method of choice for evaluating myocardial perfusion in these patients. Scintigraphy has excellent sensitivity, too, but the need to inject radioisotopes is a significant disadvantage over the course of years of repeated testing, he continued.

Diffuse myocardial perfusion abnormalities are extremely common in SSc patients. They can be detected at rest and induced by cold, high altitude, or exercise. This last observation prompted an audience member to ask whether the aggressive exercise program he and his colleagues prescribe for their SSc patients is really such a good idea.

Dr. Kahan replied that his research in the mid-1980s showed that coronary reserve in SSc patients is only half that of normal subjects. For this reason, he counsels his patients to stick to limited exercise relieved by liberal rest periods.

"I tell them to avoid dyspnea. Dyspnea means they've gone much too far. They must not exercise at too high a level because then they may induce ischemia," he said. ■

On-the-Job Exposure Doesn't Cause Wegener's

PARIS — Wegener's granulomatosis does not appear to be triggered by occupational exposure to inhaled allergens.

The hypothesis received no persuasive support from an interim analysis of a large Swedish case-control study, Dr. Ann Knight said at the annual European Congress of Rheumatology.

She reported on 2,288 Swedish patients with Wegener's granulomatosis enrolled in a national registry between 1978 and 2003. Ten controls were matched for each patient. The risk of Wegener's was then determined for patients and controls engaged in 33 occupations involving heavy exposure to dust and 5 occupations involving exposure to animals.

The overall relative risk of Wegener's granulomatosis associated with jobs involving exposure to dust was 1.1, essentially neutral.

Among the jobs were furnace worker, stone mason, smelter, paper factory worker, wood workers, glass and ceramic worker, saw operator, and flour miller.

Two occupations actually were associated with a modestly increased rate of Wegener's: miner, with a 1.9-fold relative risk, and baker, at 1.6-fold. But the numbers of subjects involved in those occupations were small, the associations weak, and the results most likely due to the play of chance, according to Dr. Knight of Uppsala (Sweden) University Hospital.

Jobs involving exposure to animals and their dander, including farmer and veterinarian, were also associated with an insignificant combined 1.1-fold relative risk of Wegener's.

Dr. Knight explained in an interview that she decided to look at occupational inhaled allergens as a potential factor in the etiology of Wegener's because the first manifestation of the disease is often in the upper airway.

Also, an earlier case-control study by Dr. Suzanne E. Lane and coworkers at Norfolk and Norwich (England) University Hospital found significantly increased risk of Wegener's granulomatosis in farmers, individuals with high occupational exposure to silica and solvents, and those with drug or other allergies (Arthritis Rheum. 2003;48:814-23). However, this study involved just 47 Wegener's patients. The Swedish study is 50 times bigger, Dr. Knight noted.

—Bruce Jancin