Helminth Exposure Tied to Immune Regulation

BY NANCY WALSH
New York Bureau

The epidemic of immune diseases that swept through the developed world during the 20th century may have resulted from a disruption in the delicate balance achieved throughout evolution between humans and certain parasitic fellow travelers, according to Dr. Joel V. Weinstock.

Diseases such as inflammatory bowel disease (IBD) were rare before the 1920s, when public health efforts began making significant strides in cleaning up the water supply, modernizing sewage treatment, and improving farming practices. While these efforts clearly had major benefits in curtailing or eliminating exposure to many disease-causing pathogens, they also had the unintended consequence of removing exposure to beneficial or even necessary organisms.

"People today live very differently than they did throughout history. People used to live close to the soil, without indoor plumbing, often with direct exposure to animals," said Dr. Weinstock, professor of medicine, Tufts Medical Center and Tufts University Sackler School of Graduate Biomedical Sciences, Boston.

The result was near universal colonization with helminths, which are complex wormlike animals that inhabit the gastrointestinal tract of mammals. Like the myriad bacteria 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 relatively harmless and, in fact, are important regulators of our immune systems.

"We have known for many years that 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," he said. 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.

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."

When other researchers were investigating possible environmental causes for the increase in these diseases, such as exposure to food dyes or from vaccinations, Dr. Weinstock took a different approach, looking for something in the environment that had been protective and had been lost. "It occurred to us that the deworming of the population—a major public health project early in the 20th century—took place at the same time as the incidence of immunologic diseases really took off," he said.

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

Because Dr. Weinstock is a gastroenterologist with a special interest in immunology, his subsequent investigations in animals and humans have focused on IBD.

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, causes a short-term colonization in the human gastrointestinal tract.

By the 12th week, 22 patients (76%) had responded to the treatment, 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.

COURTESY DR. JOEL V. WEINSTOCK

Helminth colonization appeared beneficial in Crohn's disease and other disorders.

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.

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.

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-derived medication, ASP1002, is under review by the Food and Drug Administration.

"There has been a revolution in our thinking," Dr. Weinstock said. "We have learned that we are not insulated from the world around us." ■

Natalizumab Cuts Hospitalization Rates for Crohn's Patients

BY HEIDI SPLETE
Senior Writer

SAN DIEGO — Treatment with natalizumab significantly reduced the rates of overall hospitalization and disease-specific hospitalization for adults with Crohn's disease, according to data from 1,373 adults presented at the annual Digestive Disease Week.

Hospitalization is one of the greatest expenses associated with Crohn's disease, and preventing hospitalization remains a major goal of treatment, said Dr. Bruce E. Sands, a gastroenterologist at Massachusetts General Hospital and Harvard Medical School, both in Boston.

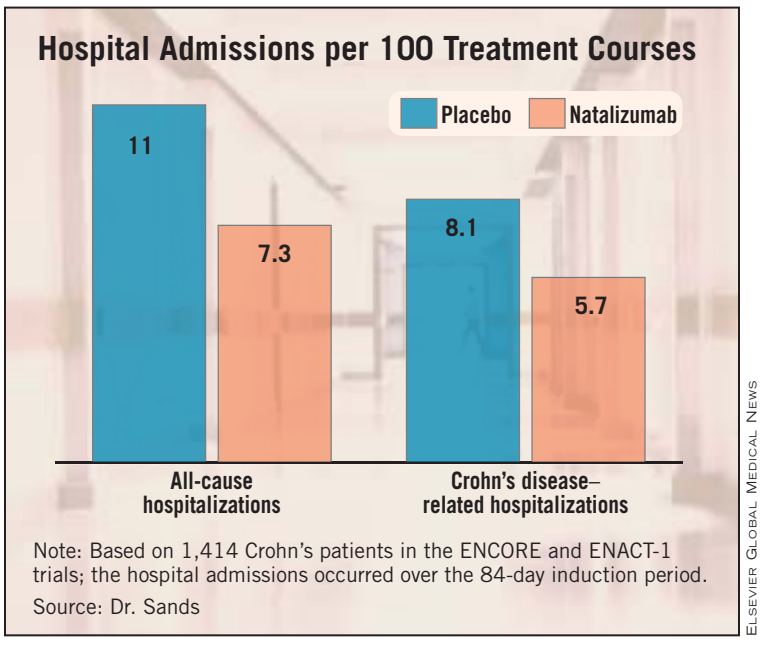
To investigate the impact of natalizumab on all-cause and Crohn's-specific hospitalizations, Dr. Sands and his colleagues analyzed pooled data from two randomized, controlled trials—ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission) and ENACT-1 (Evaluation of Natalizumab as Continuous Therapy)—which included a total intent-to-treat population of 1,414 persons.

The two patient groups had an average age of 38 years and similar demographic characteristics at baseline. The patients had been randomly assigned to receive an intravenous dose of 300 mg natalizumab or a placebo every 4 weeks for a 12-week induction period. The hospitalization rate was calculated as hospital admissions per 100 courses (per 100 patients).

The study involved an additional analysis of a subgroup of 346 patients who had failed prior anti-TNF therapy and had active inflammation, as shown by elevated C-reactive protein levels.

"We observed a total of 136 all-cause hospitalizations in the entire cohort, and of these, 109 were Crohn's related," Dr. Sands said.

In a multivariate analysis, natalizumab was associated with a significant reduction of 35% in the all-cause hospitalization rate. In addition, natalizumab use was associated with a comparable reduction of 30% in the Crohn's-related hospitalization rate, but this difference was not statistically significant.



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In the multivariate model, the effect size was even more dramatic for the subset of anti–TNF-resistant patients. The all-cause hospitalization rate in this group was significantly lower for patients who received natalizumab, compared with placebo (9.7/100 patients vs. 20.8/100 patients). The Crohn's-related hospitalization rates also were significantly lower for natalizumab patients vs. placebo patients (6.3/100 patients vs. 12.8/100 patients).

"Both anti-TNF experience and elevated C-reactive protein were associated with greater risk of hospitalization," Dr. Sands added.

In both univariate and multivariate analysis, the other independent predictors of hospitalization were low body mass index, baseline C-reactive protein level, prior anti-TNF experience, and elevation of baseline Crohn's Disease Activity Index (CDAI).

Dr. Sands has received consulting fees, grants, and research support from multiple pharmaceutical companies. ■