Novel Pathway Identified

IL-33 *from page 1*

proinflammatory cytokines and anti-collagen antibodies, they noted. Additionally, "mast cells expressed high levels of ST2 and responded directly to IL-33 to produce a spectrum of inflammatory cytokines and chemokines in vitro," confirming the hypothesis that IL-33 is a "critical proinflammatory cytokine for inflammatory joint disease," representing a possible therapeutic target for rheumatoid arthritis (Proc. Natl. Acad. Sci. USA 2008;105:10913-8).

VITALS

Major Finding: Interleukin-33 expression is implicated in early and chronic arthritis, and may represent a promising therapeutic target.

Data Source: In vitro and in vivo human and animal experiments in autoantibody-induced arthritis conducted in the biomedical research center of the University of Glasgow (Scotland).

Disclosures: Dr. McInnes has received research support or honoraria from Schering-Plough, Roche, Bristol-Myers Squibb Co., and Wyeth, and has served as a consultant for Schering-Plough and Roche.

More recently, the investigators demonstrated, for the first time, that IL-33 is required for the full induction and exacerbation of the clinical onset of autoantibody-induced arthritis, Dr. McInnes reported. They uncovered multiple mechanisms by which the molecule amplifies autoantibody-induced arthritis, including its involvement in the maturation and function of mast cells; the promotion of mast cell degranulation and associated inflammatory mediator release correlating with disease severity; and the triggering of articular proinflammatory cytokine expression.

"Our data demonstrate that IL-33 is an innate cell-derived arthritogenic factor that is able to drive both cellular and humoral arthritic responses," they wrote. This observation "provides an intriguing mechanism whereby host tissue articular cells of the fibroblast lineage can regulate and promote humoral and innate immune activation to the detriment of joint structure and homeostasis" (J. Immunol. 2010;184:2620-6).

Future studies will confirm or deny whether the IL-33 molecule is a therapeutic target in its own right, but the more important consideration might be the role played by the cellular targets for IL-33, according to Dr. McInnes. In particular, mast cells, dendritic cells, and fibroblast and endothelial cell lineages—all of which respond to IL-33—"deserve further attention," he stressed. ■

To watch a video of our interview with Dr. McInnes, go to www.rheumatologynews.com.

Single Enzyme Implicated in Periodontitis Link to RA

BY SALLY KOCH KUBETIN

NEW YORK — A single enzyme, peptidylarginine deiminase, may trigger the autoimmune process that results in rheumatoid arthritis among some people with periodontitis, Dr. Gerald Weissmann said at a rheumatology meeting sponsored by New York University.

Researchers established the association between rheumatoid arthritis and periodontal disease a decade ago (Eur. J. Med. Res. 1998;3:387-92). The same investigators went on to confirm the link, and found that the severity of RA based on a variety of markers—such as swollen joint counts, health assessment questionnaire scores, levels of C-reactive protein, and erythrocyte sedimentation rates—was directly related to the extent of periodontal bone loss in these patients (J. Periodontol. 2001;72:779-87).

The metabolic link that associates the two disorders appears to be a specific family of citrullinated proteins. These proteins have been suggested to act as an auto-antigen in RA, and autoantibodies to these proteins (anti-CCP) are highly specific for RA, according to Dr. Weissmann.

Proteins become citrullinated by the enzyme peptidylarginine deiminase, which is secreted by neutrophils, macrophages, and endothelium. Interestingly, only one bacterium, the oral pathogen *Porphyromonas gingivalis* the major cause of periodontal disease, produces this enzyme.

One of these citrullinated proteins (deiminated fibrin) may become a systemic immunogen in people who are predisposed to periodontal disease, leading to both periodontal and intra-articular inflammation. The ensuing events—involving the cascade of complement activation, phagocyte stimulation via Fc and C5a receptors, and the release of cytokines, metalloproteinases, and reactive oxygen species—ultimately result in the erosion of bone surrounding teeth and joints.

As further evidence of the link, anti-CCP titers are more predictive of joint damage at 5 years than are rheumatoid factor (RF) titers. Depletion of B cells by rituximab also lowers anti-CCP titers, and to a greater extent than it reduces RF titers (Arthritis Res. 2000;2:249-51), said Dr. Weissmann, research professor of medicine and director of the biotechnology study center at New York University.

Dr. Weissmann traced the rise of rheumatoid diseases in both England and the American colonies to the increased affordability of sugar in the late 18th and early 19th centuries. Before 1773, it was unlikely that working-class residents of the American colonies or London either had access to sugar or developed rheumatoid diseases. Access to sugar became the norm and rheumatoid arthritis became widespread only after the sugar tax was abolished in 1874, he said. ■

Disclosures: *Dr. Weissmann reported no relevant financial relationships.*

After Many Complaints, FDA to Regulate Infusion Pumps

BY ROBERT FINN

The Food and Drug Administration will regulate the design and manufacture of infusion pumps in the wake of thousands of adverse-event reports, the agency announced in a teleconference.

Over the past 5 years the FDA has received more than 56,000 reports of adverse events, including more than 500 deaths, related to the pumps. During that period there have been 87 recalls of infusion pumps undertaken to address identified safety concerns.

"Infusion pumps rank among the top of most frequently recalled devices for this 5-year period, and they are one of the top categories of devices for reporting of adverse events," Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, said during the teleconference. "There have been problems with every kind of infusion pump on the market across the entire industry. … In some cases, pumps have actually exploded in a patient's room."

The problems have ranged from manufacturing defects to software bugs to user error. Dr. Shuren described one case in which a woman who was taking the blood thinner heparin accidentally gave herself 10 times the correct dose. The culprit was "key bounce," in which someone trying to enter 20, for example, will enter 200 by mistake. The woman died.

The FDA is taking several steps to address the devices' problems at the level of manufacture.

In the interim, the agency is advising clinicians to use several strategies to reduce risk when using infusion pumps: Have a plan in place and be prepared to respond to pump failures; prevent errors by labeling infusion pump channels and tubing; check settings of infusion pumps and check patients for signs of under- or overinfusion; prevent and respond to pump problems by using available resources; and promptly report adverse events to the FDA.

The agency published draft guidance on April 23 recommending that manufacturers of infusion pumps start providing additional information on design and engineering to the agency during premarket review.

The draft guidance document, available on the FDA's Web site, is open for public comment, and the agency plans to hold a public infusion pump workshop on May 25-26.

Dr. Shuren said that the agency plans to move quickly in turning the draft guidance document into an actual set of regulations.

Among other things, the FDA recommends that each premarket submission include a structured, evidence-based discussion of all steps the manufacturer has taken to mitigate risk at each stage of the device's life cycle. That includes device design, manufacture, servicing, maintenance, and use in clinical or home settings.

'There have been problems with every kind of infusion pump on the market across the entire industry.' In some cases, pumps have actually exploded in a patient's room.

FDA inspectors will visit production facilities for the first time to examine manufacturing practices.

In addition, manufacturers will need to show that they have tested their pump in the environment in which it is intended to be used and with the types of clinicians and patients who are expected to use it.

The agency offered to help manufacturers with the task of checking the software controlling these devices. Even before premarket review, manufacturers may submit software code to the FDA, whose experts will conduct "static analysis," an automated diagnostic technique that can detect software problems early in the development process.

Dr. Shuren described the CDRH action as "a marked departure" in the way it has handled such cases in the past.

In response to a reporter's question, he noted that other medical devices have been the subject of large numbers of adverse event reports, citing implantable cardiac defibrillators as an example. ■

The FDA has established a Web site with detailed information on infusion pump problems and the agency's proposed solutions at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/default.htm.
A white paper on the Infusion Pump Improvement Initiative can be found at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/ucm205424.htm.