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FDA Panel Gives the Green Light for More Anti-NGF Testing

Fran Lowry | March 13, 2012

March 13, 2012 — The US Food and Drug Administration (FDA) Arthritis Advisory Committee has unanimously agreed to let Janssen, Pfizer, and Regeneron resume clinical trials with their respective anti–nerve growth factor (NGF) drugs, despite cases of joint destruction and osteonecrosis associated with their use.

The panel voted 21 yes, 0 no, with no abstentions, when asked whether the risk–benefit profile of the anti-NGF agents indicated a role for their ongoing development.

The drugs are being developed for the treatment of a variety of chronic painful conditions, including osteoarthritis, chronic lower back pain, diabetic peripheral neuropathy, postherpetic neuralgia, chronic pancreatitis, endometriosis, interstitial cystitis, vertebral fracture, thermal injury, and cancer pain.

Nerve growth factor promotes pain by inducing hyperalgesia in various disease states through various molecular mechanisms, resulting in sensitization of peripheral nociceptors, axonal sprouting, and sensory and sympathetic fiber innervation into damaged tissues, according to background material provided in a memo by Bob A. Rappaport, MD, director of the FDA's Division of Anesthesia, Analgesia, and Addiction Products in Rockville, Maryland.

The anti-NGF drugs attenuate this process and are considered a significant and novel strategy for the treatment of chronic pain.

In April 2010, the FDA put Pfizer's clinical trial of its anti-NGF agent tanezumab on hold after reports of unusual and unexpected cases of osteonecrosis and avascular necrosis that led to joint replacement in patients with osteoarthritis.

In December 2010, Janssen reported a case of avascular necrosis of the hip in a patient with no known history of osteoarthritis, who was given the manufacturer's anti-NGF agent fulranumab for chronic low back pain. Soon after, Regeneron's trial of its anti-NGF agent, REGN475, was halted and by January 2011, all 3 trials were put on clinical hold. Only studies in patients with terminal cancer who had intractable severe pain resulting from bone metastases were allowed to continue.

Starting Over

"This is very complex. One of the problems we are grappling with here is the quality of the data, and the reason is because the preclinical studies did not indicate that we needed to have concerns about rapidly progressive osteoarthritis, the health of subchondral bone, or concerns about joints other than the index joint," said David Blumenthal, MD, from Case Western Reserve University in Cleveland, Ohio.

"So now we're doing a post hoc, retrospective analysis trying to reconstruct what happened in these patients who appeared to have had bad outcomes," he said.

Dr. Blumenthal suggested that the sponsors go back to the drawing board and design new studies.

"We're at the start of something that's going to go on through many iterations for many years. There will be other investigational new drugs, and safety measures will have to be in place for them," he pointed out. "When you look at it from that perspective, should the people who developed this very first agent be excluded from having their drug under consideration? The possibility here, if the sponsors and the FDA are agreeable, is to start over, knowing what we know now, and taking another look in a way that maximizes patient safety."

Use for Other Painful Conditions

Robert G. Lahita, MD, PhD, from the University of Medicine and Dentistry of New Jersey in Newark, reminded the panel that there were other painful conditions besides osteoarthritis. "One of our issues is the management of cancer, in stage 4, very severe cancer pain. I don't think this should be thrown out," he said.

John Kelly, MD, from the University of Pennsylvania Health System, Philadelphia, agreed that the anti-NGF drugs could have their niche. "We can't throw the baby out with the bathwater, and I don't think we should dismiss this. It is a useful agent for some patients," he said.

Penney Cowan, the founder and executive director of the American Chronic Pain Association, from Rocklin, California, and the consumer representative on the panel, said it was important for patients with chronic pain to have some hope. She agreed that informed consent was very important for future trials, but added, "I wouldn't want to throw these agents away."

The panel also had suggestions for screening, safety monitoring, and follow-up assessments in the continuing studies.

Eric A. Walker, MD, from Milton S. Hershey Medical Center in Hershey, Pennsylvania, said obtaining baseline radiographs and magnetic resonance imaging of the pelvis are crucial.

Statistician James Neaton, PhD, from the University of Minnesota in Minneapolis, called for follow-up to be extended in every study participant out to 6 months, and even longer, and that the companies consider some sort of collaboration to combine their safety data.

Arthritis Advisory Committee Meeting. Silver Spring, Maryland. March 12, 2012.

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