Drug Monitor

Growth Hormone Can Improve Fibromyalgia Pain

Adding growth hormone (GH) to treatment for fibromyalgia can help reduce pain, with sustained effects, according to a multicenter trial carried out in 13 clinical institutions throughout Spain.

A pilot study, conducted over 12 months to cover seasonal variations in pain, had shown enough promise with GH treatment to encourage the researchers to study it further in a larger population. The current 18-month study of 120 patients, as far as they know, is the largest and longest-lasting placebo-controlled GH treatment study with fibromyalgia patients.

Patients were divided into 2 groups, given either 0.006 mg/kg/d of GH SQ (group A) or placebo (group B) for 6 months. Doses of r-GH were adjusted after months 1, 3, 7, and 9, according to centralized insulin-like growth factor 1 plasma levels or the development of adverse events (AEs) potentially related to GH. Group B patients were switched to GH treatment between month 6 and month 12. After treatment was discontinued, the patients were followed for another 6 months. All patients continued their same intensive treatment, including amitriptyline, selective serotonin reuptake inhibitors, and opioids, throughout the study.

The primary endpoint was the percentage of patients who reached fewer than 11 positive tender points. By the end of the study, more than half the patients in group A fell below that cutoff point (53% vs 33% of group B patients). Almost 40% of the patients in group A reported > 50% improvement in pain, and more than half showed > 30% improvement, as assessed by visual analog scale scores. The researchers also found a significant and clinically relevant difference between the 2 groups in all quality-of-life (QOL) scores.

The patients began to show diminishing QOL scores as early as 1 month after the treatment arm of the study ended. However, at the 18-month evaluation, those in group A still showed fewer positive tender points than those in group B. The sustained benefits of GH suggest a "memory effect," the researchers say, raising the possibility of discontinuous GH treatment.

Adding GH to the regular treatment was well tolerated. No patients withdrew from the study, and all patients followed the prescribed medication regimen. However, the study revealed a high frequency of headaches not previously reported in fibromyalgia trials of GH. Moreover, despite a low starting dose, 7% of patients had edema in their legs and feet.

Although the study wasn't designed to compare doses, their findings suggest a need for higher doses of GH in fibromyalgia than those used in classic adult GH deficiency, the researchers say. They note that about half the fibromyalgia population is premenopausal women with some estrogen capacity, which may lead to some GH resistance.

Source: Cuatrecasas G, Alegre C, Fernandez-Solà J, et al. *Pain.* 2012;153(7):1382-1389. doi: 10.1016/j.pain.2012.02.012.

Polypharmacy Puts Older Chemotherapy Patients at Risk

All patients can be at risk for AEs from taking multiple medicines. But polypharmacy can also put cancer patients at risk for less-effective chemotherapy. Then add in the age factor—older patients are vulnerable to altered pharmacokinetics, such as altered absorption.

Researchers from University Hospitals Case Medical Center; Case Western Reserve School of Medicine; and Cleveland Clinic, all in Cleveland, Ohio, say not enough is known about how polypharmacy affects older patients with cancer. Their study of 117 cancer patients aged ≥ 65 years found 80% were taking, on average, 7.3 drugs (both prescribed and nonprescribed)—a slightly higher prevalence than that found in patients without cancer. Cardiovascular drugs, CNS-acting drugs, and nonprescribed medications were the most common. About 41% of the patients were prescribed at least 1 potentially inappropriate medication.

Using performance scales, including the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), the researchers found that patients who were taking multiple medications were more likely to have poorer functional status, such as in activities of daily living.

That poor status may be secondary to AEs of medications and drug-drug interactions, the researchers say, or it could be due to the multiple comorbidities many patients had. However, they add, "interventions that target the cluster of polypharmacy, multiple comorbidities and functional status may improve treatment tolerance and ultimately translate into improved cancer outcomes for older adults."

Source: Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. *J Geriatr Oncol.* 2012;3(3):228-237. doi: 10.1016/j.jgo.2012.02.005.

Obese Women and the Vaginal Ring

Studies have suggested that obesity could make some oral and transdermal contraceptives less effective, perhaps because of differences in pharmacokinetics of contraceptive hormones. Only 1 study, however, has assessed

the impact of weight on the effectiveness of the vaginal ring, say researchers from Mailman School of Public Health, Columbia University, and Albert Einstein College of Medicine, all in New York, New York. Although that study found no effect of weight on failure rates, the researchers say, it included too few obese women to provide a clear answer.

So they conducted a study to compare pharmacokinetics and ovarian suppression in 20 women with normal weight (body mass index [BMI] between 19 and 24.9) and 20 women with BMI between 30 and 39.9. The participants received 2 vaginal rings and completed 1 ring cycle before the planned study cycle. They inserted the second ring on day 1 of the study cycle. At biweekly visits, the researchers took samples to measure ethinyl estradiol (EE_2) and etonogestrel (ENG), collecting the samples about every 3 days. Thirty-seven women completed the study.

Obese women using the vaginal ring had lower serum EE_2 levels, but the ENG levels were similar in the 2 groups. Suppression of ovarian follicle development was similar in both groups. The researchers say the lower serum EE_2 levels may explain the greater frequency of reported bleeding or spotting days in the higher-weight women.

The researchers say the physiologic results should reassure women that the ring will be effective for BMIs up to 40, but they add a caveat that, without further study in women with higher BMIs, the reassurance cannot extend to women who are morbidly obese.

Source: Westhoff CL, Torgal AH, Mayeda ER, et al. *Am J Obstet Gynecol.* 2012;207(1):39.e1-39.e6. doi: 10.1016/j.ajog.2012.04.022.

Transfusion Raises Risks for IBD Patients

Red cell alloimmunization, an adverse reaction of transfusion, may be potentiated by inflammation. And, in fact, Medical University of Vienna, Vienna, Austria, researchers have found patients with inflammatory bowel disease (IBD) who receive transfusions have more than double the risk of forming antibodies to the red blood cells.

The researchers analyzed data from 193 patients with IBD and from 357 control patients with noninflammatory diseases. Most of the patients had Crohn disease. All patients had a history of exposure to allogenic erythrocytes through at least 1 transfusion or pregnancy. The range of patients' ages at transfusion was aged 10 to 70 years, with a median age of 24. The median age of pregnancy was 32. At the time of red cell transfusion, two-thirds of the patients were on immunomodulatory therapy; about 19% required combined immunomodulatory therapy.

A "striking" 8.4% of transfused patients with IBD showed red cell antibodies—considerably more than the reported prevalence among other patient groups, the researchers say. For instance, their own control group had an immunization rate of only 3.4%.

Women had a higher risk of alloimmunization. However, the researchers found no significant influence of IBD subtype on antibody prevalence. Antibody carriers had received significantly higher numbers of red cell units, had significantly less immunomodulatory therapy at the time of transfusion, had not received double immunomodulatory therapy, and had higher lymphocyte counts.

Neither single immunomodulatory therapy nor double immunomodulatory therapy was negatively associated with antibodies. Infliximab, a tumor necrosis factor-α-blocking monoclonal antibody used to treat IBD, was previously considered to be a factor in red cell alloimmunization. Interestingly, though, the researchers say, in this study none of the 7 patients on infliximab developed antibodies.

The researchers were hampered by the fact that they couldn't precisely match control patients with the patients who had IBD: For one, the other gastrointestinal disorders affecting young patients, such as celiac disease, are not treated with transfusion. Similarly, using transfusion as a common denominator meant that the control group was older, because transfusions are mostly indicated later in life.

Because IBD often has an early onset, and because more than 10% of young IBS patients receive red cell transfusions, alloimmunization could mean a lifetime risk of associated hemolytic complications due to the high probability of repeated surgery and disease complications, the researchers point out. Moreover, young women with IBD may become pregnant, making hemolytic transfusion reaction and hemolytic disease of the fetus and newborn—the 2 major clinical implications of red cell antibodies—a major concern.

Antibodies against Rh, Kell, Duffy, and Lutheran systems were most common. In addition to restrictive transfusion strategies, the researchers advise prophylactic phenotype matching, already routine in many centers for patients with autoimmune hemolytic anemia or sickle cell anemia. Extended matching could benefit women of reproductive age, to reduce the fetal risk of later pregnancies. And finally, another option is autologous blood donation before surgery.

Source: Papay P, Hackner K, Vogelsang H, et al. *Am J Med.* 2012;125(7):717.e1-717.e8. doi: 10.1016/j.amjmed.2011.11.028.