DREAM: Dual-Release Hydrocortisone Improves NK Cell Levels in AI

Written by Emma Hitt Nichols, PhD

A once-daily, dual-release oral formulation of hydrocortisone (HC) led to significant improvement in natural killer (NK) cell levels, body weight, and systolic blood pressure in patients with adrenal insufficiency (AI) compared with patients who received conventional therapy with either cortisone acetate or oral HC. Andrea M. Isidori, MD, PhD, Sapienza University of Rome, Rome, Italy, presented data from the DREAM trial [NCT02277587].

Treatment of AI with conventional glucocorticoid therapies is associated with early mortality compared with the general population, as a result of cardiovascular disease, infection, and malignancies. A potential mechanism for this is that conventional glucocorticoid therapies do not adequately mimic circadian cortisol release, resulting in inappropriate exposure time. The purpose of the DREAM trial was to determine if a once-daily, dual-release HC tablet (DR-HC) would more closely mimic natural circadian cortisol release compared with conventional therapies.

In the single-blind, parallel, phase 4 DREAM study, 80 patients were randomly assigned to continue their conventional therapy or receive DR-HC for 6 months; interim analysis was conducted on 58 patients. Primary AI was present in 21 patients, 22 patients had secondary AI, and 15 patients served as healthy controls. All patients with AI were treated with cortisone acetate or HC upon enrollment.

At baseline, patients with AI had significantly lower levels of NK cells compared with the healthy controls (5.5%±5.7% vs 10.9%±4.2%; $P<.01$) and a trend of greater classical monocyte levels (28.9%±17.0% vs 21.5%±3.5%; $P=.08$); T-cell and granulocyte levels were similar among both groups. All patients underwent biochemical, hematologic, and metabolic assessments at 0, 3, and 6 months.

At the 3-month analysis, patients with AI who received DR-HC experienced a significant increase in NK cells (+5.2±7.4; $P<.01$) compared with patients who received conventional therapy (cortisone acetate or HC; +0.8±5.9) or healthy controls (+1.0±3.4). The improvement occurred regardless of primary vs secondary AI or type of glucocorticoid treatment at enrollment. In addition, patients who received DR-HC experienced significant improvement in body weight ($P<.01$) and systolic blood pressure ($P<.05$), as well as a trend toward decreased HbA_{1c} levels ($P=.07$), compared with patients who received conventional therapy.

Prof Isidori stated that the difference in monocyte levels between the DR-HC and conventional therapy arms may be immune suppression as a result of a difference in bioavailability of the agents; however, the significant increase in NK cell levels in patients treated with DR-HC refuted this mechanism, suggesting that a chronobiological effect was the most likely explanation. In addition, Prof Isidori suggested that improvement in NK cell levels in patients with AI is an important finding because NK cells play a critical role in fighting infections and malignant cells.

VIDOS: Vitamin D Supplementation Does Not Improve the Incidence of Falls

Written by Emma Hitt Nichols, PhD

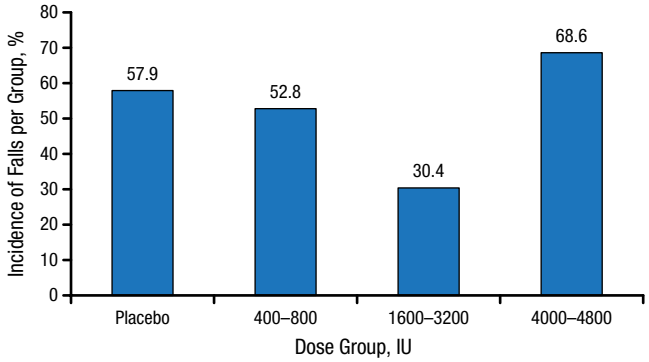
Elderly women who received 1600 to 3200 IU QD of vitamin D supplementation experienced a lower incidence of falls compared with women who received lower or higher doses of vitamin D or placebo, but overall differences were not significant. Shervin Yousefian, MD, Creighton University, Omaha, Nebraska, USA, presented data from the VIDOS study [NCT00472823].

Results regarding the effect of vitamin D supplementation on falls and physical performance in elderly patients have been inconsistent. The purpose of VIDOS was to evaluate the effect of vitamin D supplementation on falls and physical performance in vitamin D–deficient postmenopausal women living in the community.

In this interventional study, 163 postmenopausal white women were randomly assigned to receive vitamin D supplementation with 400, 800, 1600, 2400, 3200, 4000, or 4800 IU QD or placebo for one year. Women were required to be vitamin D deficient, with a serum 25-hydroxyvitamin D (25[OH]D) level of ≤20 ng/mL. The mean age of the 147 women who completed the study was 66.2 years and the mean body mass index was 30.3 kg/m^2. Patients were excluded if they had active nephrolithiasis, chronic kidney or liver disease, persistent hypercalcemia, or a medical condition prohibiting physical activity or if they had a disease or were receiving medication that affected calcium or bone metabolism. Accounting for data from 7-day food diaries, calcium supplementation was administered to achieve a daily calcium intake of 1200 mg.

In the placebo arm, patients who did not experience falls had greater serum levels of 1,25 dihydroxyvitamin D ($1,25[OH]_2D$) than patients who did experience falls. Patients who received vitamin D supplementation

Figure 1. Incidence of Falls Stratified by Vitamin D Supplementation Dosage



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demonstrated higher levels of $1,25(OH)_2D$ compared with patients who received placebo, but there was no significant difference in $1,25(OH)_2D$ levels between patients who did or did not experience falls, regardless of the amount of supplementation. Similarly, 25(OH)D levels increased in a dose-response fashion among patients who received supplementation; however, there was no significant difference in 25(OH)D levels between patients who did or did not experience falls.

The fall rate varied among the arms of the trial. Patients in the placebo arm and those patients who received 400 to 800 IU QD of vitamin D experienced similar fall rates (Figure 1). However, the fall rate was considerably lower in patients who received 1600 to 3200 IU QD of vitamin D, whereas patients who received the largest dose of vitamin D had an even higher fall rate.

The timed up and go (TUG) value was slower at 1 year among all arms; however, patients who received 1600 to 3200 IU QD or 4000 to 4800 IU QD of vitamin D appeared to have a slower rate of increase in the TUG value. At 1 year, there was no significant difference in the chair stand test among all of the arms.

In conclusion, the results of the VIDOS study suggest that, overall, vitamin D supplementation did not appear to improve physical performance or the incidence of falls. However, Dr Yousefian pointed out that there was a U-shaped distribution for the incidence of falls among the various doses of vitamin D supplementation, suggesting that there may be an optimal dose for fall prevention at about 2000 IU QD. However, additional larger studies are needed to better assess the role of vitamin D supplementation in the incidence of falls among elderly patients.

Liraglutide Leads to Increased Weight Loss Response in Patients Without Diabetes

Written by Rita Buckley

In the phase 3, double-blind, randomized SCALE–Obesity and Prediabetes trial [NCT01272219], significantly more obese and overweight adults without diabetes mellitus were weight loss responders when treated with liraglutide, 3 mg, rather than placebo. Weight loss responders also had improvements in glycemic control, cardiometabolic outcomes, and quality of life. The SCALE–Obesity and Prediabetes trial was a subanalysis of the SCALE study, a large phase 3 clinical program investigating the safety and efficacy of liraglutide, 3 mg, for weight management in people with and without diabetes.

Patrick O'Neil, PhD, Medical University of South Carolina, Charleston, South Carolina, USA, presented the results of the subanalysis. Overweight (body mass index [BMI] ≥ 27 kg/m^2 with ≥ 1 comorbidities) or obese (BMI ≥ 30 kg/m^2) patients without diabetes mellitus were randomized to liraglutide, 3 mg (n = 2487), or placebo (n = 1244) as an adjunct to diet and exercise. Overall baseline characteristics included a mean age of 45 years, a body weight of 106 kg, and a BMI of 38 kg/m^2.

The analysis compared key efficacy and safety outcomes of responders (≥ 5% weight loss at week 56 from baseline) vs nonresponders (< 5% weight loss at week 56 from baseline). At week 56, significantly more individuals on liraglutide vs placebo were weight loss responders (63.2% vs 27.1%; $P < .0001$). Mean weight loss for responders vs nonresponders on liraglutide was –11.7% vs –1.7%. In the placebo group, the respective figures were –10.0% vs +0.1%. Liraglutide was also associated with a greater reduction in waist circumference in responders vs nonresponders (–11.0 vs –3.3 cm). Respective figures in the placebo group were –10.0 vs –1.7 cm.

Fasting plasma glucose was lower for responders in the liraglutide vs placebo group (–8.3 vs –2.8 mg/dL). For nonresponders, the figures were –5.0 vs +1.1 mg/dL. In liraglutide vs placebo responders, respective reductions in systolic blood pressure were –5.5 vs –3.4 mm Hg. Nonresponders in both groups had respective findings of –2.0 vs –0.8 mm Hg. Change in overall physical health scores on the SF-36 Health Survey Update questionnaire for liraglutide vs placebo responders was +4.3 vs +4.1; for nonresponders, the respective outcomes were +2.1 vs +1.3.

The most common adverse events (AEs) were gastrointestinal related. These were higher in liraglutide vs