Gastroenterology 2023;165:301–303

# GASTRO DIGEST

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## Obeying the Law: Energy Balance in Alternate-Day Fasting, Exercise, or Both Together in Patients With Obesity and NAFLD

*Ezpeleta M, Gabel K, Cienfuegos S, et al.* Effect of alternate day fasting combined with aerobic exercise on nonalcoholic fatty liver disease: a randomized controlled trial. Cell Metab 2023;35:56–70.e3.

The First Law of Thermodynamics states that energy can neither be created nor destroyed, only altered in form. Simply put, energy balance in obesity comprises input and expended energy. Lifestyle interventions for patients with obesity, insulin resistance, and nonalcoholic fatty liver disease (NAFLD) often address both aspects of energy input ("diet") and energy expenditure ("exercise"). Perhaps out of expediency, "diet and exercise" are recommended as if this represents a single intervention. Yet, either intervention by itself often represents a major personal upheaval. As a result, adherence to either intervention alone, let alone in combination, can be difficult and short-lived. This raises a few clinically important questions. Could we achieve desired metabolic effects by inaugurating a single intervention, and if so, which one? What is the adherence and durability of the intervention?

Ezpeleta et al recently compared the efficacy of short-term interventions on several metabolic parameters in adults with obesity and NAFLD (defined as magnetic resonance proton density fat fraction >5%). They randomized 80 patients to explore the effect of alternate-day fasting (ADF) alone (600 kcal/d alternating with *ad libitum* feeding), exercise alone (5 days/wk, 60-minute supervised aerobic activity session at 60%–85% maximum heart rate), a combination of the two, or no intervention.

Overall, 3-month combination therapy induced improvements in multiple metabolic parameters (intrahepatic triglycerides, body weight, fat mass, waist circumference, and several markers of insulin resistance) vs control and exercise-only groups, but it was not more effective at improving any of the measured metabolic outcomes vs ADF alone. Moreover, 85% and 95% of patients in the ADF and combination groups, respectively, desired to continue ADF after the protocol ended, whereas 25% attrition was observed in the exercise-only group,

The data give a rare and detailed comparison between intervention groups, with high adherence to intense ADF and supervised routine aerobic exercise over a brief interval. Limitations include small sample sizes (n = 20 per group), and a larger sample size may better resolve the efficacy of these interventions. The data, however, are informative regarding attrition in the exercise-only group, 25%, even in a motivated and closely observed population. Thus, although ADF monotherapy compared more favorably overall vs diet and exercise, and although adherence was high in this intervention, one might not yet conclude unequivocally that ADF monotherapy is to be recommended where combination therapy is unattainable. Nevertheless, the data do demonstrate that time-limited intensive combination diet and exercise intervention improves multiple body morphometry and liver fat better than exercise, but not better than ADF alone on the same measures. And although each patient's individual intervention is always tailored to their disposition, tolerance, and clinical needs, these data are some of the first to allow more fully informed clinical decisions to treat obesity, NAFLD, and their complications by intervening on energy balance. The data will certainly be informative, at least for now, while we remain beholden to the laws of thermodynamics.

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## Bepirovirsen—A New Therapy for Chronic Hepatitis B Infection

*Yuem M-F, Lim S-G, Plesniak R, et al.* Efficacy and safety of bepirovirsenin chronic hepatitis B infection. N Engl J Med 2022;387:1957–1968.

Despite the existence of an effective vaccine, chronic hepatitis B virus (HBV) infection remains a major cause of liver-associated morbidity and mortality. Current antiviral therapies based on nucleoside or nucleotide analogues (NAs) achieve HBV "control" by inhibiting replication, but only a minority of patients (<5%) achieve functional cure defined as HBV surface antigen (HBsAg) loss.

Bepirovirsen is an anti-sense oligo-nucleotide targeting HBV-RNA transcripts. In this phase 2b trial, the efficacy and safety of weekly subcutaneous bepirovirsen injections for 12 or 24 weeks was investigated. The primary efficacy outcome was HBsAg (and HBV-DNA) loss during the 24 weeks after study drug discontinuation. The study comprised 457 participants (49% receiving NA therapy). After 24 weeks of bepirovirsen therapy, 9% to 10% of patients achieved HBsAg loss, whereas the response rates were lower in the 12-week (1%–3%) and placebo arm (0%). No differences were found regarding NA therapy or HBeAg status. However, among HBeAg-positive participants, the primary outcome event occurred only in those on NA therapy (6% vs 0%). Low HBsAg levels at baseline (<3000 IU/mL, approximately two-thirds of the cohort) were associated with a higher functional cure rate. The latter indicates that HBsAg loss is easier to achieve in a benign phase of the infection when HBsAg production from integrated HBV DNA is at its lowest levels.

Several notable findings highlight the need for a better understanding of bepirovirsen's mechanism of action. First, alanine transaminase (ALT) elevations were frequent (41% with and 17% without NA). Because concomitant NA therapy did not exclude the possibility of ALT flares, the latter may reflect immune-mediated cytolysis, especially if HBsAg levels also decrease. Although most ALT flares resolved without evidence of liver dysfunction, this might prevent treatment in patients with advanced liver disease (excluded from this study). The most common adverse events were mild injection-site reactions in 50% to 70% of patients. However, another side-effect to be considered is a drug-class (anti-sense oligo-nucleotides) vascular inflammation and complement activation, which occurred in 55% of patients and adds to the complexity of routine monitoring (ie, evaluating C3 and C4 levels and urine tests to discard drug-induced renal injury).

Finally, "blips," or single-time-point increases in HBsAg or HBV-DNA occurred after bepirovirsen discontinuation in patients reaching the primary outcome. That finding highlights the importance of the follow-up period in HBV clinical trials and raises the question of the durability of treatment response. Whether this is due to the sensitivity of the assay or the complexity of the HBV life cycle, HBV integrations, and interplay with the immune system remains to be determined.

Larger trials and longer follow-up are needed to assess the safety and efficacy of bepirovirsen as well as the durability of off-treatment response. Safety and efficacy should be balanced against current NA therapies, which are associated with lower cost, oral availability, and minimal side-effects. In addition, a careful selection of patients with a higher probability of response (HBeAg negative, under NA therapy, and low HBsAg levels) will be key. Nevertheless, the future seems promising for patients living with chronic HBV infection.

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# Dupilumab: The New Kid on the Block for Management of Eosinophilic Esophagitis

*Dellon E, Rothenberg ME, Collins MH, et al.* Dupilumab in adults and adolescents with eosinophilic esophagitis. N Engl J Med 2022;387:2317–2330.

Eosinophilic esophagitis (EoE) is a chronic and progressive immune-mediated disease affecting children and adults. Mainstay treatment of active EoE has included proton pump inhibitor (PPI) therapy, swallowed topical corticosteroids, and food-elimination diets, with the goal of controlling inflammation and reducing symptoms, albeit with variable response rates. The immuno-pathogenesis of EoE, characterized by type 2 helper cell inflammation, highlights therapeutic potential of antiinflammatory medications.

A 3-part, phase 3, international, multi-center trial evaluated the efficacy of dupilumab in patients 12 years of age and older with active EoE despite 8 weeks of high-dose PPI. Dupilumab is a human monoclonal antibody that blocks interleukin-4 and interleukin-13 and has been approved for the treatment of type 2 inflammatory conditions such as atopic dermatitis, asthma, and chronic rhinosinusitis. In this study, parts A and B were independent 24-week randomized, double-blind, placebo-controlled trials. Primary end points were histologic remission (≤6 eosinophils per high-powered field) and absolute change in the Dysphagia Severity Questionnaire.

In part A, 81 patients were randomized 1:1 to receive dupilumab at 300 mg weekly (n = 42) or matching placebo (n = 39). Both primary and all secondary end points were significant in part A. Specifically, histologic remission at week 24 occurred in 25 (60%) of those that received weekly dupilumab vs 2 (5%) who received placebo (adjusted between-group difference of 55 percentage points; $P < 0.001$).

In part B, 240 patients were randomly assigned 1:1:1 to receive dupilumab 300 mg weekly (n = 80) or every 2 weeks alternating with weekly placebo (n = 81), or placebo weekly (n = 79). Histologic remission occurred again in approximately 60% of patients receiving dupilumab (47 [59%] with weekly dupilumab and 49 [60%] with dupilumab every 2 weeks) compared with 5 (6%) with placebo. Incidence of adverse events was 60% to 86% across trial groups, predominantly related to injection-site reaction. No deaths were reported.

These landmark phase 3 randomized placebo-controlled trials highlight the therapeutic efficacy of weekly 300 mg dupilumab in terms of histologic remission and symptom reduction among adults and adolescents with EoE despite high-dose PPI therapy, as well as dupilumab's overall favorable safety profile. However, because active EoE is known to require active treatment, it is not entirely surprising that dupilumab out-performed placebo. Knowledge gaps regarding the efficacy of dupilumab compared with standard treatments for EoE such as topical corticosteroids, which may be more accessible and affordable to patients compared with dupilumab, persist. Nonetheless, the recent