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

Food and Drug Administration approval of dupilumab in May 2022 (representing the first U.S.-approved drug for EoE) and positive results from these independent trials heralds a new and exciting paradigm of therapy for EoE.

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Conflicts of interest
The author discloses the following: Dr Yadlapati reports consulting for Medtronic, StatLinkMD, and Medscape, consulting for and research support from Ironwood Pharmaceuticals, consulting for and institutional support from Phathom Pharmaceuticals, and advisory board membership and stock ownership with RJS Mediagnostix. Dr Yadlapati is the principal investigator for National Institutes of Health grant K23 DK125266.

Can Microbes and Their Components Prevent Growth Failure Caused by Malnutrition?

Schwarzer M, Gautum UM, Makki K, et al. Microbe-mediated intestinal NOD2 stimulation improves linear growth of undernourished infant mice. science 2023;379:826–833.

Undernutrition and growth failure remain critical global health challenges, impacting mostly young children and leading to significant morbidity and mortality. Intestinal microbes are certainly impacted by diet, but they have also been shown to impact growth in human and animal studies. For example, germ-free mice display poor growth with low levels of insulin and insulin-like growth factor-1 and introducing microbial communities reverses these effects; malnourished children improve with a microbiota-directed therapeutic diet. Interestingly, even a single bacterial strain (*Lactiplantibacillus plantarum*; LP^{WJL}) has been shown to rescue the effects of undernutrition in mice, but mechanisms have remained unclear.

In a recent study published in *Science*, Schwarzer et al provide exciting and detailed evidence on how microbes could salvage growth using a unique mouse model, with clear mechanistic insight. First, an isocaloric, low-fat/protein malnourishment juvenile mouse model was developed, which showed weight, length, and bone development failure with decreased production of hepatic insulin-like growth factor-1 and insulin. Administering LP^{WJL} to these mice partially (but significantly) rescued all growth-related parameters, in both sexes and across 2 mouse strains. Response to LP^{WJL} was strain specific; another LP strain did not improve growth.

To investigate which component of these bacteria was mediating these effects, the authors then showed that heat-killed LP^{WJL} were still able to improve growth, and in fact isolated bacterial cell wall alone was sufficient to produce benefit. But what in the cells wall mediates this effect? Using an in vitro cell model, various innate pattern recognition molecules were transfected and NOD-2 (which senses cell wall peptidoglycan and is linked to Crohn disease) was stimulated by LP^{WJL} but not the other LP strain. Convincingly, undernourished NOD-2 knockout mice failed to respond to LP^{WJL}. An associated increase in epithelial cell renewal, mediated by type 1 interferon, was observed using a transcriptomic approach. The essential role for NOD-2 was attributed to the intestinal epithelium because the beneficial effect was lost in a gut-specific conditional NOD-2 knockout, but not when NOD-2 was removed from hepatocytes.

Taken together, this article offers a comprehensive and appealing case where a single bacterial component can rescue growth failure owing to malnourishment through well-defined pathways (some of which remain to be explored). Beyond the solid scientific contributions of this work in defining the complex interplay between diet, gut microbes, host epithelial renewal, and systemic metabolic pathways, there are tremendous clinical and public health implications. Obviously, the best solution for undernourishment is improved food access, but supplementation with microbes, or even specific microbial components, or other downstream manipulation of these identified pathways, could be effective. Additional indirect implications could include altering other gut epithelial renewal defects, such as tissue recovery from injury, on the one hand, or cancer, on the other. Such basic discoveries are essential to advance knowledge and introduce novel therapeutic approaches for future clinical research.

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