Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 54-year-old woman with invasive ductal carcinoma of the breast and well-controlled chronic plaque psoriasis presented to the emergency department with a 2-day history of painful rash and fever. Five days before the onset of the rash, the patient had completed a 2-week course of systemic glucocorticoids to treat side effects of chemotherapy. The body temperature was 38.2°C, and heart rate 137 beats per minute. On physical examination, widespread erythematous patches with overlying, coalescing pustules were seen on the torso, arms, legs, face, and scalp, with sparing of mucosal surfaces. Laboratory testing was notable for neutrophilic leukocytosis and an elevated C-reactive protein level. Biopsy of the rash in the periumbilical region revealed neutrophil-rich pustules in the epidermis on histopathological testing. What is the most likely diagnosis? You are offered: Acute generalized exanthematous pustulosis, Generalized pustular psoriasis, IgA Pemphigus, Staphylococcal scalded skin syndrome, and Subcorneal pustular dermatosis. It is what it looks like. Nerandomilast is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory effects. In a phase 2 trial involving patients with idiopathic pulmonary fibrosis, treatment with nerandomilast stabilized lung function over a period of 12 weeks. In a phase 3, double-blind trial, investigators randomly assigned patients with idiopathic pulmonary fibrosis to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo, with stratification according to background antifibrotic therapy (nintedanib or pirfenidone vs. none). The primary end point was the absolute change from baseline in forced vital capacity (FVC) at week 52. Nerandomilast reduced the decline in FVC, compared to placebo. The same hypothesis was next tested in patients with progressive pulmonary fibrosis, which includes a variety of known causes. Again, nerandomilast reduced the the decline in FVC in these patients over 52 weeks (50 ml decrease compared to 150 ml decrease). In both studies, the most common side effect was diarrhea, which did not result in treatment discontinuation. Oxyntomodulin is another incretin hormone that agonizes both the GLP-1 and Glucagon receptors.

Mazdutide is a synthetic oxyntomodulin analog given subcutaneously weekly. Evidence suggests that incretin-based dual agonist pharmacotherapy is helpful in persons with obesity (as we have seen from many studies). Mazdutide, a glucagon-like peptide-1 and glucagon receptor dual agonist, may have efficacy in persons with overweight or obesity. In a phase 3, double-blind, placebo-controlled trial in China, investigators randomly assigned, in a 1:1:1 ratio, adults 18 to 75 years of age who had a body-mass index of at least 28 or had a BMI of 24-28 plus at least one weight-related coexisting condition to receive 4 mg of mazdutide, 6 mg of mazdutide, or placebo for 48 weeks. The obese patients dropped 10 to 15% of body mass while the placebo patients stayed the same. Side effects were tolerable and the same with other incretins. Adeno-associated virus (AAV)–mediated gene therapy has emerged as a promising treatment for hemophilia B (factor IX deficiency). Data on safety and durability from 13 years of follow-up in a cohort of patients who had been successfully treated with AAV-factor IX gene therapy are now available. Indeed, the AAV-mediated gene therapy was remarkably effective for over a decade. Two unrelated cancer cases showed up but could not be attributed to the treatments and would be expected based on chance alone. Carbamoyl-phosphate synthase-1 (CPS-1) is the initial step in removing ammonia via the Krebs urea cycle. We next inspect a remarkable case report of an infant born with a CPS-1 mutation. Over the course of 6 months the mutation was identified, hepatic cell lines with the mutation were generated, a Crispr-Cas construct was prepared, mouse lines of CPS-1 mutations had by that time been generated, safety was proved in primates, and the child was treated with a positive result. The N Engl J Med review is on malnutrition in the elderly. The weekly case report involves a man with an increasing nasopharyngeal mass, hearing loss, facial palsy, over eight months and an unexpected (for me) diagnosis. In the Lancet we confront small-cell lung cancer. A randomized trial of lurbinectedin (a novel alkylator) and atezolizumab (PD-1) provides a better outcome than atezolizumab alone, even in terms of overall survival. Anal-canal cancer is associated with papilloma virus and when advanced very difficult to treat. In a randomized, controlled phase 3 trial, retinfanlimab (PD-1) with carboplatin and paclitaxel provided an improved outcome compared to conventional chemotherapy. Carpal tunnel syndrome is conventionally treated operatively but could steroid injections be as good? This idea was tested in a

randomized controlled trial, but the results suggested that we had better stick with the operation. Rheumatic fever was a classic and common diagnosis in my generation. Lancet reviews this condition of classic molecular mimicry. In Science Magazine we learn through experiments in cultured infected red blood cells and rodent models as well as by examining human data, that unconjugated bilirubin serves a host-beneficial function during *Plasmodium* infection. In the Washington Post we are informed about the Death Clock artificial intelligence AP that tells us how much longer we will live. As an octogenarian, this AP of course interested me. Join me on Tuesday, June 17 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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