Dear friends of clinical journal club - load the latest 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.

An 82-year-old man presented after being “found down.” One week earlier, he had returned from a 1-month visit to Chad, his country of birth, and had started having weakness. His body temperature was 37.4°C, and his blood pressure was 88/47 mm Hg. The physical examination was notable for confusion. Laboratory studies showed a hemoglobin level of 12 g per deciliter (reference range, 13.5 to 17), an elevated lactate dehydrogenase level, thrombocytopenia, metabolic acidosis, and acute kidney injury. A peripheral-blood smear is shown (revealing erythrocytes with “ring forms”). Which of the following is the most appropriate next step in management? You are offered: Chloroquine phosphate, Exchange transfusion, Oral artemether-lumefantrine, Oral atovaquone-proguanil, and Parenteral artesunate. Rather a moving target but for today only one answer is correct. Polymyalgia rheumatica is a common inflammatory disease characterized by pain and stiffness in the shoulders and hips. Glucocorticoids are the first-line treatment, but relapses and glucocorticoid-related toxic effects are common, which underscores the need for effective alternatives. Secukinumab is a fully human monoclonal antibody that selectively inhibits the driver, interleukin-17A. Investigators enrolled patients with recently relapsed polymyalgia rheumatica and randomly assigned them to receive secukinumab at a dose of 300 mg (SEC-300 group), secukinumab at a dose of 150 mg (SEC-150 group), or placebo for 52 weeks. Patients in all the groups also received prednisone on a tapering schedule for 24 weeks. The primary outcome was sustained remission at week 52. Even with secukinumab, less than half achieved sustained remission, but secukinumab beat placebo. Persons carrying loss-of-function variants of proprotein convertase subtilisin–kexin type 9 (PCSK9) have reduced levels of low-density lipoprotein (LDL) cholesterol and fewer atherosclerotic cardiovascular disease events than persons without such variants. VERVE-102 is an investigational base-editing therapy (knockout strategy) designed to durably inactivate the PCSK9 source in the liver. Investigators administered one intravenous infusion of VERVE-102 at one of six doses to adults with heterozygous familial hypercholesterolemia or premature coronary artery disease.

VERVE-102 consists of a messenger RNA encoding an adenine base-editor protein and a guide RNA targeting PCSK9, which are encapsulated in a lipid nanoparticle incorporating N-acetylgalactosamine. The objectives were to assess safety and changes in blood PCSK9 protein and LDL cholesterol levels. Knocking out PCSK9 seems to work; ALT and AST were elevated but tolerability appeared good. The RET protooncogene is mutated in about 2% of patients with non-small-cell lung cancer (NSCLC). Selpercatinib, a highly selective, potent, and central nervous system–penetrant RET inhibitor, is already approved for RET fusion–positive advanced or metastatic NSCLC. The efficacy and safety of selpercatinib in early-stage NSCLC are unknown. Investigators conducted a phase 3, double-blind trial involving patients with RET fusion–positive NSCLC who had received definitive therapy with curative intent (surgery or radiotherapy with adjuvant systemic anticancer therapy, if applicable). Patients were randomly assigned to receive adjuvant selpercatinib or placebo for up to 3 years. The primary end point was investigator-assessed event-free survival. In these 2% of NSCLC patients selpercatinib increased event-free survival. GPRC5D is an orphan G-protein-coupled receptor (of unknown function) expressed on plasma cells. Talquetamab, a bispecific antibody targeting GPRC5D and CD3, has led to durable responses in patients with heavily pretreated relapsed or refractory multiple myeloma in phase 1–2 trials, with a limited effect on normal B cells. In a phase 3 trial, investigators randomly assigned patients with relapsed or refractory multiple myeloma who had previously received at least one line of therapy to receive talquetamab plus daratumumab and pomalidomide (Tal-DP), talquetamab plus daratumumab (Tal-D), or daratumumab plus pomalidomide and dexamethasone (DPd). The primary end point was progression-free survival. The talquetamab groups met the primary endpoint. The tobacco companies preside over a >$350 billion dollar per year business. The N Engl J Med concerns evidence-based tobacco-cessation strategies for low- and middle-income countries. Good luck! The N Engl J Med mystery patient is a young woman that presents to an emergency room with an elevated anion gap. Six hours later, some decisions are made. In the Lancet, we learn about zenagamtide. Zenagamtide is a dual GLP-1-receptor and amylin-receptor agonist. In a randomized trial against placebo in type-2 diabetics, daily oral zenagamtide had dramatic effects on HbA1C and reduced body weight by >10%. In a second trial, subcutaneous weekly

zenagamtide had a similar dramatic effect in type-2 diabetic obese patients. Non-segmental vitiligo is an auto-immune disease that involves destruction of melanocytes. The process involves cytokine (JAK-STAT) signaling. Upadacitinib is a janus-kinase inhibitor. In a randomized trial upadacitinib beat placebo with acceptable side effects in stopping and reversing non-segmental vitiligo The Lancet review is on retroperitoneal fibrosis, an IgG4 disease. We learn that the pathogenesis is highly complex and involves many cells and processes. In the differential diagnosis is the Erdheim Chester disease. This CD68-positive histiocytosis features a BRAF v600e mutation, implying malignancy. In Science Magazine, we encounter a massive genomic, single-cell sequencing investigation elucidating mechanisms causing hypertension, alas solely in rats. The Washington Post reports on a UK-biobank-based study, indicating that even 3 minutes of exercise lowers the risk of 13 cancers. Load down the file and join me again on August 19, 16:00 English and 17:00 German.

Sincerely, Fred Luft

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