gene in bone marrow stem cells, 1,2 resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis, 3. Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release4 . Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure5 . Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems6 . Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma7,8,9. Platelet activation, complementmediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH. 10 Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.11 The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion) has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.12,13 Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.14,15 Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.16,17

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HOW WE (WILL) TREAT PNH?

Semra AYDIN

Department of Oncology, Hematology, Immuno-Oncology and Rheumatology, University Hospital of Bonn, Bonn, Germany

Clinical signs arising from intravascular hemolysis, hemolysis-related transfusions and thrombosis are indications for treatment initiation in paroxysmal nocturnal hemoglobinuria (PNH), whereas clone size *per se* is not. Eculizumab prevents intravascular hemolysis and reduces significantly thromboembolic risk resulting in a five-year overall survival of >90%. Hemoglobin value, LDH and reticulocyte count are used to define treatment response. Residual intravascular hemolysis is mainly caused by an incomplete C5 blockage and can lead to continuous low–grade hemolysis or transient breakthrough hemolysis episodes in 10-15% of PNH patients. Additional complement–amplifying conditions such as infections, surgery or pregnancy may overcome efficient therapeutic levels of Eculizumab and therefore require dose adjustments. *C3–mediated extra–vascular hemolysis* represents the main reason for residual anemia during anti–C5 treatment. Patients with an inherited C5-variant lack response to Eculizumab and have been directed (in past) towards allogeneic HSCT. Transplantation has an overall mortality of up to 30%, with a higher risk in patients with previous thrombosis. A plethora of novel therapeutic agents are reported to impact on both; residual intravascular hemolysis and C3–mediated extra–vascular hemolysis. The new C5 inhibitor Ravalizumab with an eight–week i.v. dosing interval showed non-inferiority to Eculizumab. Crovalimab, binding on the single missense C5 heterozygous mutation is injected s.c. monthly; two large phase III trials are ongoing as add on- and mono-therapy. Others, such as Pozelimab, injected subcutaneously on a weekly basis after an initial IV loading dose or Tesidolumab are still under current investigation. Currently investigated proximal inhibitors are acting towards: (i) the C3 complement; (ii) complement factor D or (iii) the complement factor B. They are aiming in particular to prevent C3–mediated extra–vascular hemolysis. Pegcetacoplan is a PEGylated version of compstatin which binds to C3 and is injected s.c. in monotherapy 4 weeks after initial concomitant therapy with Eculizumab. In a recent phase III trial, pegcetacoplan showed superiority to eculizumab in hemoglobin change from baseline and is now approved by the FDA for patients with PNH who are either treatment–naive or switching from anti–C5 monoclonal antibodies. Danicopan is an oral first–in–class factor D complement alternative pathway inhibitor and decreased significantly transfusion requirement, as shown in a phase II trial (phase III ongoing). BCX9930, another FD inhibitor in early development is given orally and demonstrated initial clinical efficacy both as add–on therapy in patients with inadequate response to eculizumab as well as in monotherapy in treatment–naive patients. In conclusion, novel proximal and distal complement inhibitors with different application modalities, in part as add-on or monotherapy seem to improve significantly intra- and extra–vascular hemolysis in PNH, resulting in a better hematological benefit. Before choosing specific treatment, hematologists have to assess hemolysis, thrombosis and patients‘ bone marrow function. Future studies will help to explore long-term efficacy and safety of these novel agents.

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THE THEN, NOW, & FUTURE OF ENGINEERED T-CELL THERAPEUTICS FOR HUMAN APPLICATION

Bruce Levine, Ph.D.

The University of Pennsylvania, Philadelphia, PA