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Review Article

Post ASH 2022: Paroxysmal Nocturnal Hemoglobinuria and thrombotic microangiopathies

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ABSTRACT:

This review of the most important abstracts on paroxysmal nocturnal hemoglobinuria (PNH) and thrombotic microangiopathies presented at the latest American Society of Hematology (ASH) Meeting shows that relevant research to complement inhibition is ongoing. Clinical trials for PNH are studying the physical function, fatigue, and QoL scores of novel treatments as an alternative to eculizumab.

Currently phase III studies (crovalimab for Chinese PNH, inhibitor naïve patients, and sutimlimab for C1 inhibition in cold-agglutinin disease) of new complement inhibitors are examining the long-term effect, and safety of these new licensed therapies. Further studies in larger populations with long follow up are needed to describe the personalized-medicine treatment algorithms in complement-mediated diseases.

Thrombotic thrombocytopenic purpura patients are the population assessed concerning silent cerebral infarction, and under caplacizumab treatment for their cognitive function, fatigue and quality of life. Moreover, patients with sickle cell disease (SCD) are evaluated with modern assays for complement activation. SCD complications presented with complement activation even in the steady state of the disease.

KEY WORDS: *Paroxysmal nocturnal hemoglobinuria, thrombotic microangiopathies, complement, cold-agglutinin disease, thrombotic thrombocytopenic purpura*

INTRODUCTION

The complement is a unique system involved in natural immunity. Genetic mutations and autoantibodies that lead to its unregulated activation participate in the pathogenesis of various diseases. Among them, paroxysmal nocturnal hemoglobinuria (PNH) remains the prototypical disease of complement activation and inhibition.[1] The first complement inhibitor, eculizumab, was initially approved in 2007 for the treatment of PNH and subsequently for diseases such as atypical hemolytic uremic syndrome (aHUS), Myasthenia Gravis, and Neuromyelitis Optica. Preclinical and clinical studies have shown the need to introduce the next generation of complement inhibitors. In light of new therapeutic developments, this review aims to describe the current knowledge in the pathobiology and treatment of complement – mediated diseases.

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Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare, acquired hematopoietic cell disorder characterized by abnormal terminal complement activa-

tion, which causes intravascular hemolysis (IVH) and increases the risk of thrombosis.[1,2] PNH patients treated with C5 inhibitors often manifest extravascular hemolysis (EVH), and symptomatic anemia, which results in packed Red Blood Cells (pRBCs) transfusions. PNH also manifests with extreme fatigue, which negatively affects the patients' physical functioning and health-related quality of life (HR-QoL). The treatment of PNH requires complete inhibition of the terminal complement pathway.[3] Thus, inhibition of Factor D, an enzyme of the alternative complement pathway, may improve anemia, a result of EVH and IVH, and requirement of transfusions.[4,5]

Crovalimab

Crovalimab, a new C5 inhibitor, demonstrated complement inhibition in Chinese, C5 inhibitor naïve, PNH patients in the COMMODORE 3 study, presented at ASH. 51 patients received the agent in doses based on weight, including loading (intravenous and subcutaneous) and maintenance (subcutaneous) doses. Clinically benefitted patients continued treatment after the 24 weeks of study. Primary endpoints were met: 78,7% (95% CI: 67,8-86,6%) of patients achieved hemolysis control, with LDH reaching ≤ 1.5 × ULN by the third week of treatment. Transfusion avoidance, in terms of transfusion reduction of pRBCs per patient, was meaningfully significant ($P < 0.0001$), from a mean 10,8 pRBC (SD: 6,6) to 4,6 (SD:6,7). Moreover, hemoglobin stabilization was achieved by 26 patients (51%), and clinical improvement in fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue – FACIT score) was accomplished by the second week. High patient tolerance was demonstrated, as no treatment was discontinued due to treatment-emergent adverse events (TEAEs). However, a patient sustained a subdural hematoma after a fall, a unique Grade 5 incident. Grade 3-4 adverse events also occurred as one patient developed bile duct stones, another an abdominal wall mass, and a third bacteremia. 47,1% of patients developed upper respiratory tract infections (Grade 2), and 11,8% had a weight gain.[2]

ABP 959

ABP 959 is a humanized monoclonal antibody currently being developed as a biosimilar agent to eculizumab. A recent study evaluated efficacy and safety of this molecule in a comparative, randomized, double-blinded, crossover clinical trial in adult PNH patients. PNH patients, previously stable on eculizumab 900mg twice per month, were randomized to receive either 900mg of ABP 959 (period 1, or 52 weeks) and then 900mg of eculizumab (period 2, or 26 weeks) or 900mg of eculizumab (period 1) and then 900mg of ABP 959 (period 2). Clinical similarity between the two agents was established by comparison of one-sided 97,5% upper confidence interval (CI) limit for the geometric least square mean ratio of LDH, which was measured in the 27th week, for ABP 959 and eculizumab with a 2,873 non – inferiority margin. Total complement, total hemoglobin, haptoglobin, bilirubin, and type III erythrocytes were all stable during the study and comparable between the two arms. One patient in the eculizumab-first group discontinued, due to non-serious asthenia and fatigue (Grade 2). The safety profile between the two agents was comparable, and immunogenicity results during the first period were similar between ABP 959 and eculizumab. Patients tested negative in both groups for binding, neutralizing, and treatment-boosted anti-drug antibodies (ADAs).[6]

Pozelimab (human monoclonal antibody and C5 inhibitor) and Cemdisiran (N-acetylgalactosamine-conjugated small interfering RNA -siRNA)

The combination of these two agents is currently evaluated in an ongoing randomized, phase 2 study in a sample of 22 PNH patients, who were previously treated with pozelimab. Both treatment groups received 200mg cemdisiran subcutaneously once a month and pozelimab 400mg also subcutaneously either once or twice a month. During the study participating patients completed the FACIT questionnaire, the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire global health status (GHS)/QoL and physical functioning questionnaires. PNH patients who received both pozelimab and cemdisiran, especially in the once a month regimen, showed improved and sustained physical function, fatigue and GHS/QoL scores compared to their pre-treatment scores.[7]

Vemircopan (ALXN2050)

Inhibition of Factor D, an alternative complement pathway enzyme, effectively controls hemolysis and reduces transfusion needs. An oral agent of factor D inhibition, danicopan (ALXN2040), was successful when administered alone and as an add-on to eculizumab in reducing anemia and subsequent transfusions. However, it showed less control of IVH as a monotherapy in some PNH patients.

Vermicopan (ALXN2050) was tested as a monotherapy in PNH in a phase 2 study of 12 weeks (NCT04170023) in three groups of PNH patients, treatment naïve, eculizumab pre-treated and change from danicopan monotherapy. All patients received 120mg vermicopan twice daily (BID) – which could be increased up to 180mg if hemoglobin had not increased more than 1 g/dL by the fourth week of treatment, if pRBCs were required, and if LDH >1,5

ULN by the end of the second week. In this study, mean hemoglobin increased by 3,9 g/dL (1,11) (from 7,9 (1,29) to 11, 8 (1,25)), LDH decreased by 78% in the first two weeks of treatment, reticulocyte count fell from 212,4 (86,47) x 103/uL to 120 (51,44) x 103/uL and FACIT score improved by 13 points. No treatment withdrawals, serious TEAEs (≥ grade 3), or deaths were reported in this small sample of patients. Headache was reported most often (36,4%). Dose escalation to 180mg in 7 out of 9 patients resulted in elevated hemoglobin levels.[1]

Cold – Agglutinin Disease (CAD)

Cold agglutinin disease is a chronic, rare, autoimmune hemolytic anemia defined by classical complement pathway activation and subsequent hemolysis. Sutimlimab (SUT) is humanized monoclonal antibody that halts the classical pathway activation by C1 inhibition, has been approved for CAD treatment. The part A of phase 3 of the CADENZA study showed that CAD patients treated with SUT had fast and sustained amelioration in hemoglobin, hemolysis markers, and patient-reported quality of life (QoL).[8] Part B, an extension of the CADENZA study, demonstrated the long-term efficacy and safety of the treatment of CAD patients with SUT.[8)] and the long-term effect of SUT on CAD patients' quality of life.[9]

CAD patients with no recent blood transfusions, who had completed part A, received SUT twice weekly for at least one year. Changes in hemoglobin, hemolysis markers, FACIT scores, pRBCs transfusions, and pharmacodynamic markers were included in the efficacy data.[8] Patient-reported outcomes were assessed with questionnaires such as FACIT- Fatigue, 12-Item Short Form Health Survey (SF-12), Patient Global Impression of Fatigue Severity (PGIS), and Patient Global Impression of Change from baseline (PGIC).[9]

7/39 patients did not complete part B of the study, with one due to TEAEs. Hemoglobin levels and FACIT scores increased in part A and were sustained in part B (>11 g/dL). The increases correlated with C4 normalization and almost complete classical pathway inhibition. Bilirubin levels were normalized in part A and were sustained in part B.[8] CAD patients on SUT in Part A had a significant improvement in FACIT scores, which were sustained in part B, whereas patients on placebo in part A had a positive change in FACIT scores in part B, upon beginning SUT treatment. Scores on the SF-12 questionnaires improved meaningfully and were maintained throughout part B. 93,3% of patients reported a consistent improvement in the PGIC scores at week 87. PGIS was boosted, from 46,7% of patients stating none or mild fatigue to 78,6% at week 87.[9]

During part B, nine patients (23,1%) received more than one transfusion. Most patients (92,3%) experienced one or more TEAEs. 2 patients with underlying risk factors for thromboembolism presented with thromboembolic events, although both were regarded as unrelated to SUT treatment. One urinary tract infection (≥ grade 3) was reported. No serious hypersensitivity events or meningococcal infections were observed.[8]

Narsoplimab in High-Risk Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (HSCT-TMA)

Thrombotic microangiopathy in the HSCT environment develops through the activation of the complement pathway and coagulation cascade. Narsoplimab (OMS721) is a fully human IgG4 monoclonal antibody, acting as an inhibitor of MASP-2 (Mannan-binding lectin serine protease 2), a lectin complement pathway enzyme. Treatment with narsoplimab in adults with HSCT-TMA produced significant clinical response, prolonged survival, and was overall well tolerated.[10,11] A recently presented Phase 2 clinical trial design will assess the efficacy and safety of narsoplimab in 18 pediatric HSCT-TMA patients.[12]

Thrombotic thrombocytopenic purpura (TTP)

Acquired thrombotic thrombocytopenic purpura is an immune – mediated deficiency of the ADAMTS 13, a von Willenbrand factor cleaving enzyme. The ADAMTS13 deficiency enables unprohibitied adherence of von Willenbrand factor to platelets, thus inducing microthrombosis, thrombocytopenia, hemolytic anemia and tissue ischemia. Treatment with caplacizumab, a targeted therapy, prohibits the adhesion of von Willenbrand factor to platelets resulting in decreased incident of major thromboembolic events, TTP-related death incidence, and TTP recurrence.[13]

A recent multi-center study evaluated the real-world outcomes of caplacizumab treatment on 66 TTP patients and compared them to a control group of 44 TTP patients.[14] Patients on caplacizumab treatment had lower hemoglobin, more comorbidities, albeit less neurological sequalae. This study showed updated data of the safety and effectiveness of caplacizumab in TTP disease, in plasma-exchange naïve patients, in plasma-exchange refractory disease and after re-administration.[14]

Survivors of immune TTP often present with declined cognitive function and significant fatigue, impacting the patients' quality of life.[15] Moreover, they have elevated cardiovascular risk, including a stroke.[16] A recent study that evaluated the fatigue and cognition of iTTP patients in remission recruited 101 patient. Fatigue and cognition scores were worse in the iTTP group, compared

to the general US population, breast cancer, and severe COVID-19 survivors, but similar to systemic lupus erythematosus (SLE) patients. This study also showed that iTTP survivors in the long term (more than 5 years since their last episode) are still struggling with fatigue and cognition.[15]

The prospective "Neurologic Sequelae of TTP – NeST" study assessed the prevalence, risk factors of silent cerebral infarction (SCI), and possible associations of the SCI with cognition. The 32 iTTP survivors who completed the study were subjected to annual brain MRI - checking for brain lesions indicative of SCIs - were evaluated with the NIH ToolBox Cognition Battery, examining cognitive function (executive, processing speed, episodic and working memory, language) and with the Beck Questionnaire for depression.

The NeST study showed that cognitive decline is associated with SCI in iTTP survivors; mild was present in 23,1% and major in 30,8% of patients. Executive function and processing speed were more frequently affected. SCI patients did not present higher depression scores than non-SCI patients, thus excluding depression as a confounding factor in the SCI and cognition association.[16]

Invasive fungal diseases (IFD) in the post-cellular therapy era

Treatment of benign and malignant disorders includes cellular therapies, such as gene therapy, CAR-T cell, autologous and allogeneic hematopoietic cell transplantation (HCT). IFDs increase morbidity and mortality in adult patients treated with cellular therapies. A series of possible contributing factors to the IFD incidence were analyzed in a recent study that included 950 recipients of cellular therapies. In particular, the study showed that none of the 19 CAR-T cell and none of the two gene therapy patients developed IFD, while 3/456 autologous HCT patients presented with probable IFD. Multiple fungus species were detected, such as candida, mucormycosis, fusarium, and aspergillus in the 52 IFD (possible, probable and proven) patients, despite caspofungin (primary prophylaxis) and amphotericin (secondary prophylaxis) in the aplastic period, followed by posaconazole and isavuconazole in the immunosuppressive period. The analysis showed that independent risk factors for IFD were the donor type and the moderate/severe chronic graft versus host disease (GVHD). Five-year overall survival (OS) was meaningfully decreased in IFD patients, while IFD predicted OS independently of other risk factors such as donor type and chronic GVHD. The study concluded that proven IFD associates with poorer outcomes in allogeneic HCT patients and that possible IFD presents with similar patient results to probable IFD.[17]

Complement activation in Sickle Cell Disease (SCD)

Morbidity and mortality in SCD remain despite recent developments in its treatment. Recent studies showed complement activation in SCD complications, such as the delayed hemolytic transfusion reaction (DHTR), thus implying that complement inhibition may present as a suitable treatment for those patients. A recent study examined if the novel functional assays are applicable in detection of complement activation in SCD complications, and if the SCD patients have uninvestigated, unique, clinical, or genetic characteristics.

Consecutive SCD adult patients were recruited, based on specific eligibility criteria. Samples were collected at enrollment and at any change of their disease during the one-year follow-up period. The 81 samples were examined for complement activation with C5b-9 and modified Ham test, and with next generation sequencing analysis for other complement factors (eg. CFI, CFB, CFD, etc).

During follow-up, 23 patients had a disease update (17 with vaso-occlusive crises and 6 with proteinuria). SCD complications presented with complement activation even in steady state, with elevated levels of C5b-9 and positive modified Ham test, followed by a C5b-9 significant decrease in the follow up period. Genetic testing revealed 25 rare variants as well as 5 deleterious variants. Patients with deleterious variants had increased complement activation and a meaningfully elevated transfusion needs. In conclusion, complement inhibition may present as a suitable therapy in SCD patients, particularly when developing SCD complications.[18]

CONCLUSION

This review of the most important abstract on PNH and thrombotic microangiopathies presented at the latest American Society of Hematology (ASH) Meeting showed that relevant research is ongoing. Further studies in larger populations with long follow up are needed to describe the personalized-medicine treatment algorithms in complement-mediated diseases.

Conflict of Interest: Nothing relevant to declare.

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