ASH Highlights and Commentary: Blood Disorders

Brad Lewis, MD, of Machaon Diagnostics, discusses the implications of three recent studies on acquired hemophilia, thrombotic thrombocytopenic purpura (TTP), and hereditary hemorrhagic telangiectasia (HHT). A small trial on acquired hemophilia found that emicizumab reduced mortality, while a TTP study suggested that silent cerebral infarctions could be a marker for stroke risk and treatment aims. Finally, a trial on VAD044 for HHT showed promising results in reducing epistaxis and improving hemoglobin levels, marking the potential for the first dedicated therapy for this commonly overlooked bleeding disorder.

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Emicizumab Prophylaxis Instead of Immunosuppression During Early Management of Acquired Hemophilia A

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Acquired hemophilia A (AHA) is a severe bleeding disorder caused by autoantibodies (also called inhibitors) that neutralize coagulation factor VIII (FVIII), leading to an increased risk of life-threatening bleeding events. The standard treatment involves immunosuppressive therapy (IST) aimed at eradicating these inhibitors. Although IST achieves remission in 60% to 80% of patients, it is frequently associated with adverse effects, particularly infections, which remain a leading cause of mortality in AHA patients in Western countries.

EMICIZUMAB AS AN ALTERNATIVE EARLY TREATMENT

The GTH-AHA-EMI study, conducted from March 2021 to June 2022, used emicizumab as a prophylactic alternative to IST during the initial management of AHA. Emicizumab, a bispecific monoclonal antibody that mimics FVIII function, was administered for the first 12 weeks to prevent bleeding episodes, allowing for the delay of IST initiation. This approach aimed to reduce the risk of infection and improve survival rates.

STUDY DESIGN

This long-term analysis compared outcomes between patients from the GTH-AHA-EMI study (n = 47) who received emicizumab with delayed IST, and a historical cohort from the GTH-AH 01/2010 study (n = 101) who underwent immediate IST upon diagnosis. The key endpoints included partial remission (PR), complete remission (CR), incidence of adverse events, and overall survival over 2 years.

Partial remission was defined as FVIII activity recovery to over 50% without bleeding episodes. Complete remission was defined as PR alongside a negative inhibitor test, prednisolone tapered to less than 15 mg/day, and discontinuation of any additional IST.

RESULTS

In the GTH-AHA-EMI group, 44 of the 47 patients continued observation beyond week 12. Of

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these, 19 patients (43%) extended emicizumab prophylaxis for a median of 21 weeks, and notably, 8 patients never initiated IST. Two of the patients died early after week 12, and six patients achieved spontaneous PR.

In the GTH-AHA-EMI cohort, 35 patients (80%) eventually commenced IST, most of them between weeks 12 and 24. Among these, 83% achieved PR (median 30 weeks) and 80% reached CR (median 38 weeks). Comparatively, the historical cohort undergoing immediate IST achieved PR in 84% (median 4 weeks) and CR in 61% (median 10 weeks), indicating that while time to remission was longer in the emicizumab group, overall remission rates were higher.

Delayed IST was associated with a lower incidence of severe infections. In the GTH-AHA-EMI cohort, 31% of patients receiving IST experienced infections, none of which were life-threatening or fatal. In contrast, the historical cohort reported infections in 36% of patients, including 17 fatal cases.

Propensity score-matched analysis revealed superior survival rates in the emicizumab group. One-year survival was 86% vs. 69% in the immediate IST cohort, and two-year survival was 82% compared to 63%. The hazard ratio for overall survival was 0.39 (95% CI: 0.19–0.80, p = .011), demonstrating a reduction in mortality risk with emicizumab prophylaxis and delayed IST.

CONCLUSION

Promisingly low rates of severe infection and mortality were reported at end of study after 24 weeks with emicizumab. The findings support using emicizumab as initial prophylaxis in AHA management, allowing for postponing IST and reducing the risk of treatment-related complications.

Perspectives for the Advanced Practitioner

Brad Lewis, MD, Machaon Diagnostics

Acquired hemophilia is a disorder caused by antibodies that inhibit factor VIII. It is conceptually similar to immune thrombocytopenic purpura, except now the antibodies are directed against the VIII molecule, and it causes a very severe bleeding disorder. It tends to happen in people of any age, particularly in older patients, often in patients with associated autoimmune disease, malignancy, or sometimes after surgery. It carries with it a very high mortality due to both infections and bleeding.

Current therapies exist, but they all carry a significant risk of thrombosis. They are also somewhat difficult to administer. The efficacy cannot be easily assessed, and they are certainly not convenient to use. This study, then, is very intriguing.

It began in March of 2021 and ended recently. During the study, patients were given emicizumab during the first 12 weeks of therapy, and then they were given an immunosuppressive regimen of choice to get rid of these antibodies. This compares to the current treatment, where immunosuppressive therapy is given from the beginning and prothrombotic therapy is given when needed throughout the patient's management. At the end of the study at 24 weeks, they could ask to extend the emicizumab.

This is now the 2-year follow-up. They compared their results to immunosuppressive therapy alone with the traditional therapies for bleeding. Emicizumab is a bispecific antibody that essentially replaces factor VIII. It does not cause any prothrombotic events; it simply steps into the cascade and replaces factor VIII.

There were 47 patients in this study. The endpoints of the study were either a partial response with greater than 50% factor VIII levels or a complete response where the inhibitor disappeared entirely and factor VIII levels returned to normal. At the end of the study, 44 patients remained on therapy. Forty-three percent of them continued to a median of 21 weeks. Eight never started immunosuppressive therapy—two because they died early, and six had spontaneous partial remissions occurring right around week 40.

Eighty percent of the patients started immunosuppressive therapy at around 12 weeks, using the usual steroids, rituximab, cyclophosphamide, mycophenolate, or various combinations. Eighty-three percent went on to achieve partial remission, and 80% went on to achieve a complete remission. Thirty-one percent of these patients had 12 infections; none of these were life-threatening.

In the control arm from 2010, 84% achieved partial remission, 61% achieved complete remission, and 36% had 55 infections, with 17 of those fatal, for a survival rate of only 63% vs. no deaths in this small emicizumab trial, other than the two before therapy started.

Implications for the Advanced Practitioner
Emicizumab appears to be effective in acquired factor VIII deficiency. There is lower mortality, at least in this small preliminary study, than with traditional prothrombotic therapies. Spontaneous partial remissions and complete remissions occurred, and immunosuppressive therapy appears to be better tolerated when it is begun after the initial bleeding presentation has been stabilized in these patients. Obviously, this needs to be repeated with a larger study.
Disclosure: Dr. Lewis has served on the speakers bureau for Alexion Pharmaceuticals and is an employee of Machaon Diagnostics.

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Silent Cerebral Infarction as a Potential Predictor of Stroke in Immune TTP Survivors

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Immune thrombotic thrombocytopenic purpura (iTTP) is a rare, life-threatening blood disorder characterized by the formation of small clots throughout the body, leading to reduced platelet counts and organ damage. Patients are also at increased risk for complications, particularly cerebrovascular disease. In addition to stroke, silent cerebral infarctions (SCIs), which are brain lesions detected on MRI without obvious neurological symptoms yet associated with cognitive impairment, are found in over 50% of iTTP survivors.

The Neurologic Sequelae of TTP (NeST) study aimed to investigate whether SCIs progress during periods of clinical remission in iTTP survivors and whether such progression increases the risk of overt stroke.

METHODS

The NeST study prospectively enrolled adult patients diagnosed with iTTP, identified by ADAMTS13 enzyme activity levels below 10% during an acute episode. Participants were monitored annually during clinical remission with neurological assessments using the NIH Stroke Scale and brain MRIs to detect SCIs. SCI was defined as an infarct-like lesion, at least 3 mm in size, identified on MRI (T2 and FLAIR hyperintensity) without corresponding neurological symptoms.

To quantify SCI burden, researchers applied the modified Age-Related White Matter Changes (ARWMC) scale, which rates white matter hyperintensities across multiple brain regions on a scale from 0 to 30. The study assessed SCI progression over 1 year using the Wilcoxon signed-rank test and evaluated stroke risk in patients with and without SCIs at baseline.

RESULTS

As of March 1, 2024, 40 iTTP survivors had completed their baseline assessments, with 26 participants undergoing follow-up MRIs 1 year later. The median age was 48 years, with 78% of participants being female and 75% identifying as Black. Many participants had common cardiovascular risk factors, including hypertension (39%) and diabetes (19%), and 18% had previously experienced a stroke during iTTP episodes.

At baseline, SCIs or white matter lesions were detected in 77% of participants, with a median ARWMC score of 4. Over the course of remission—defined as a median period of 13 months between MRIs—SCIs were found to be progressive in 38.5% of participants. Notably, this progression occurred despite the absence of clinical iTTP relapse or ADAMTS13 enzyme decline. The median ARWMC score increased significantly from 2 to 2.5 (p = .002), indicating that cerebral injury continued even during clinical remission.

Age emerged as a significant risk factor for SCI progression, with older participants more likely to develop new or worsening brain lesions. This association remained significant even after

adjusting for hypertension, diabetes, prior stroke, and ADAMTS13 activity levels.

During a median follow-up of 37 months, 15% of participants (6 out of 40) experienced overt strokes. All strokes occurred in participants who had SCIs at baseline, with none reported in individuals without initial SCIs. Furthermore, the stroke rate was significantly higher in participants with progressive SCIs (30%) compared to those whose SCIs remained stable (0%, $p = .020$).

CONCLUSION

The NeST study revealed that SCIs in iTTP survivors continue to progress during remission, even in the absence of clinical disease activity or ADAMTS13 relapse. Patients with SCIs are at an increased risk of future overt strokes. Specific risk factors could be targeted to prevent SCI progression, and SCI may be used as an endpoint in clinical trials evaluating new therapies for iTTP.

Perspectives for the Advanced Practitioner

Brad Lewis, MD, Machaon Diagnostics

Thrombotic thrombocytopenic purpura, or TTP, is an autoimmune or congenital decrease in the ADAMTS13 protein. In the absence of ADAMTS13, patients develop episodic platelet clumping and an associated occlusion of the microvasculature and the thrombotic microangiopathy. Traditionally, prior to therapies, this disorder had a 90% mortality. Now with our improving therapies, including plasma exchange, immunosuppression, and even recombinant ADAMTS13 for congenital TTP, that mortality has dropped to about 10%. Partial remission is common and is widely accepted as an appropriate target, often with a very low 5% to 10% ADAMTS13 activity but when there are no symptoms and there are no recurrent episodes of TTP.

Recent studies, including the Neurologic Sequelae of TTP study (the NeST study), showed silent infarctions in TTP patients during their therapy. A Dutch study showed an increased risk of stroke in the normal population who have the lower quartile of ADAMTS13, which again is about 50% of normal levels. This has raised the question of what the appropriate target for response to therapy in TTP is.

This study looked at acquired TTP patients during their annual evaluations after their initial therapy. They were evaluated with the NIH stroke scale and also with an MRI where they used the modified Age-Related White Matter Changes (ARWMC) scale to assess possible progression of lesions. Silent cerebral infarction is a punctate 3-millimeter T2 lesion without associated stroke deficits.

Forty patients made it to their first annual visit. Twenty-six made it to their second annual visit. The median age was about 48. Forty percent had hypertension, and 20% with diabetes. Twenty percent had a stroke during their initial TTP flare. There were no relapses of TTP during this post-study period. NIH stroke scale was zero for all at the beginning of the study and at the end of the study.

Silent cerebral infarction lesions were seen in 77% of patients. Forty percent of patients developed new lesions after their therapy during their follow-up despite not having any episodes of TTP documented. The median ARWMC score increased by two. Stroke was seen in 0% of those without any silent cerebral infarction lesions. Twenty percent of patients who had a silent cerebral infarction at baseline had a stroke, and 30% who saw not only a silent cerebral infarction at baseline but then had progression went on to have a stroke.

Implications for the Advanced Practitioner

This is a small study, but it is quite consistent with other data that is beginning to come in from all over right now. It suggests that silent cerebral infarction may be a good endpoint for future studies of new therapies. It suggests that progressive silent cerebral infarctions and stroke in remission may require new criteria for what remission really is—perhaps a higher ADAMTS13 target than we are currently targeting. And finally, it suggests following silent cerebral infarctions clinically as a way to identify patients at high risk of stroke so that there can be interventions both in their TTP and in their other lifestyle-associated risk factors.

Disclosure: Dr. Lewis has served on the speakers bureau for Alexion Pharmaceuticals and is an employee of Machaon Diagnostics.

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Assessing the Safety and Efficacy of the Novel Allosteric AKT Inhibitor VAD044 in Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT) is the second most common inherited bleeding disorder, affecting approximately 1 in 5,000 individuals. Despite its prevalence, there are currently no approved disease-modifying therapies.

Hereditary hemorrhagic telangiectasia is characterized by severe, recurrent nosebleeds (epistaxis), chronic gastrointestinal bleeding, and arteriovenous malformations (AVMs) in visceral organs. These complications contribute to significant clinical and psychosocial morbidity, leading to reduced life expectancy. The underlying pathophysiology involves mutations in genes like endoglin or ALK1, which result in overactivation of the AKT signaling pathway. This promotes telangiectasia formation and AVMs.

VAD044, an oral allosteric AKT1/2 inhibitor, has emerged as a potential disease-modifying therapy for HHT. This proof-of-concept (POC) randomized, multicenter study aimed to evaluate VAD044 in moderate to severe HHT.

METHODS

This study enrolled 75 adult patients with moderate to severe HHT. Inclusion criteria were more than 20 episodes of epistaxis lasting over 80 minutes per month, an Epistaxis Severity Score (ESS) above 4, and a history of IV iron infusions or red blood cell transfusions within the previous 6 months.

Participants were randomized in a 1:1:1 ratio to receive either VAD044 at 30 mg, VAD044 at 40 mg, or a placebo, taken orally once daily for 12 weeks. An additional 8-week follow-up period was included to monitor safety and efficacy outcomes. The primary endpoint focused on the safety and tolerability of VAD044, assessed by the frequency and severity of adverse events (AEs). Secondary and exploratory endpoints examined changes in epistaxis severity, frequency, duration, the number of epistaxis-free days, hemoglobin levels, and patient-reported outcomes using the Patient Global Impression of Change (PGIC) scale.

Seventy-five participants, with a mean age of 56 years and mostly female (57%), were enrolled. Of these, 24 patients received VAD044 at 30 mg, 25 received 40 mg, and 26 were assigned to the placebo group. Six patients discontinued treatment due to adverse events.

SAFETY AND TOLERABILITY

VAD044 was generally well tolerated, with adverse events mostly mild to moderate in severity. Grade 1 AEs occurred in 83% of patients in the 30 mg group, 75% in the 40 mg group, and 65% in the placebo group. Grade 2 AEs were reported in 46%, 54%, and 31% of the respective groups. Grade 3 AEs were similar across groups, occurring in 17%, 13%, and 15% of patients. All serious AEs were deemed unrelated to the study drug.

Common on-target, dose-related AEs included rash, hyperglycemia, and diarrhea. Rash was the most frequent side effect, affecting 25% of the 30-mg group and 46% of the 40-mg group, compared to 8% in the placebo group. Most rashes were mild and managed with topical corticosteroids without discontinuing the drug. Hyperglycemia was observed in 12% of patients in the 40 mg group, while diarrhea was reported in both VAD044 groups but remained mild and manageable.

EFFICACY

VAD044 demonstrated promising efficacy, particularly at the 40 mg dose. Patients in this group experienced significant reductions in epistaxis frequency, duration, and flow intensity by 33%, 43%, and 17%, respectively. In comparison, the placebo group showed more modest reductions of 17%, 17%, and 7%. Epistaxis-free days increased by an average of 5 days per month in the 40 mg group, compared to 2.7 days in the placebo group.

The 40-mg dose met predefined meaningful change thresholds for reductions in epistaxis frequency, duration, and increased epistaxis-free days, while the placebo did not. Patient-reported outcomes further supported these findings.

Perspectives for the Advanced Practitioner
Brad Lewis, MD, Machaon Diagnostics

Hereditary hemorrhagic telangiectasia (HHT) is the second most common inherited bleeding disorder. It is an autosomal dominant disorder occurring in about 1 out of 5,000 people. Previously, there has been no real dedicated systemic therapy. It can be caused by mutations in several genes, most of them involving mutations in genes like endoglin or ALK1. It results in recurrent mucosal bleeding, and epistaxis is often severe. Occult GI bleeding can happen. Visceral bleeding can happen as well, with large vascular malformations causing symptoms. There can be symptomatic lesions in the lungs, liver, and brain. Symptoms develop over time, often starting in early teenagerhood, but they can start much later and progress throughout life.

This is a commonly missed disorder, for example, as a cause of refractory iron deficiency, and the diagnosis is becoming more and more important as therapies are developed. It can be diagnosed clinically, especially if the patient has a family history, or with genetics, which are effective although not perfect.

Current therapy is symptomatic: iron to replace iron deficiency, cautery and surgical procedures, topical therapies like tranexamic acid and propranolol, and, if necessary, radiologic or even surgical approaches to some of the arteriovascular malformations. With little trial data, systemic recommendations have been made, including bevacizumab, pomalidomide, and other immunomodulatory drugs, but all of these have prothrombotic side effects.

VAD044 is an oral daily inhibitor of the AKT1 and 2 enzymes. This was a randomized controlled study in both the EU and in the US looking at the safety and tolerability in patients with moderate to severe HHT, defined as greater than 20 episodes of epistaxis or greater than 80 minutes of bleeding per month and/or the requirements for IV iron or packed red blood cells in the preceding 6 months. With these criteria, 75 patients were randomized to three different groups. One group received the drug VAD044 at 30 mg, one group received it 40 mg daily, and the other group was a placebo group. This went on for 12 weeks with an 8-week follow-up.

The results: six patients discontinued their therapy. There were grade one and two adverse events common in all three groups. It was felt that perhaps the rash, diarrhea, and hyperglycemia might be drug related. These are known side effects, but the incidence of side effects was similar in all three groups. Grade three adverse events occurred in 15% but were equally distributed through all three groups. None of them were felt to be related to the drug.

The response was obtained by evaluating epistaxis frequency, duration, and epistaxis-free days, and all of these improved significantly. There was a global impression scale, and patients felt that they were much better 60% of the time with the 40 mg, 35% of the time with 30 mg, and 17% of the time with the placebo. At 12 weeks, there was a 1 g hemoglobin difference between the 40-mg treatment group and the placebo group, and there were felt to be visible regressions of lesions.

Implications for the Advanced Practitioner

This is the first-ever novel therapy being developed specifically for HHT, and it appears to be safe, tolerable, and potentially effective in a preliminary trial. What this study really does, in my mind, is to remind you to look ever more carefully for this very common and commonly missed disorder, which can present to us as refractory iron deficiency. This is only the first of a number of new dedicated therapies that look like they are going to be coming out in the near future.

Disclosure: Dr. Lewis has served on the speakers bureau for Alexion Pharmaceuticals and is an employee of Machaon Diagnostics.