

reparative phenotype, suggesting that cell-free DNA and chromatin potentiate and extend inflammation at sites of tissue injury and delay healing. Although the mechanisms through which cell-free DNA and chromatin hinder tissue repair extend beyond the scope of this Brief Report, histone-complexed DNA fragments do correlate with endothelial cell damage, coagulopathy, and mortality in pediatric trauma patients.⁸

Finally, an interesting question raised by this study is whether non-NETing neutrophils in the inflammatory milieu, sterile or otherwise, acquire similar capabilities to aid in the clearance of DNA-containing debris from ongoing NET formation by a subset of neutrophils recruited to the area of injury. With the link between failed clearance of self-DNA debris and autoimmune disease clearly demonstrated,⁹ failure of neutrophil-mediated self-DNA debris clearance, as demonstrated in this model, could contribute to an increased risk for autoimmune disease in patients with inflammatory syndromes and NET formation. It will be interesting to see whether non-NETing neutrophils are “prepared and finished” by the inflammatory milieu to clear the NETotic debris.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

- Oved JH, Paris AJ, Gollomp K, et al. Neutrophils promote clearance of nuclear debris following acid-induced lung injury. *Blood*. 2021;137(3):392-397.
- Potey PM, Rossi AG, Lucas CD, Dorward DA. Neutrophils in the initiation and resolution of acute pulmonary inflammation: understanding biological function and therapeutic potential. *J Pathol*. 2019;247(5):672-685.
- Németh T, Sperandio M, Mócsai A. Neutrophils as emerging therapeutic targets. *Nat Rev Drug Discov*. 2020;19(4):253-275.
- Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. 2020;136(10):1169-1179.
- Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134-147.
- Wang J, Hossain M, Thanabalasurir A, Gunzer M, Meininger C, Kubes P. Visualizing the function and fate of neutrophils in sterile injury and repair. *Science*. 2017;358(6359):111-116.

- Paris AJ, Liu Y, Mei J, et al. Neutrophils promote alveolar epithelial regeneration by enhancing type II pneumocyte proliferation in a model of acid-induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2016;311(6):L1062-L1075.
- Russell RT, Christiaans SC, Nice TR, et al. Histone-complexed DNA fragments levels are associated with coagulopathy, endothelial cell

- damage, and increased mortality after severe pediatric trauma. *Shock*. 2018;49(1):44-52.
- Atianand MK, Fitzgerald KA. Molecular basis of DNA recognition in the immune system. *J Immunol*. 2013;190(5):1911-1918.

DOI 10.1182/blood.2020009101

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THROMBOSIS AND HEMOSTASIS

Comment on Knoebl et al, page 410

Future directions in acquired hemophilia A

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In this issue of *Blood*, Knoebl et al have prospectively evaluated the effects of emicizumab for bleeding control in 12 patients with acquired hemophilia A (AHA), a rare autoimmune bleeding disease that requires prompt diagnosis and urgent treatment.¹

The pathogenesis of AHA, which usually occurs in adults and the elderly, consists of the production of neutralizing autoantibodies that inhibit the function of coagulation factor VIII (FVIII). In ~50% of cases, AHA is associated with an underlying (often occult) pathology such as autoimmune disease, cancer, or graft-versus-host disease after allogeneic bone marrow transplantation. Symptomatic patients require immediate management of acute bleeding, inhibitor suppression or eradication, and treatment of any underlying disease.

Three agents are currently licensed for bleeding control in AHA²: recombinant activated FVII (rFVIIa), activated prothrombin complex concentrate (APCC), and recombinant porcine FVIII (rpFVIII). There are no studies that compare these treatments, so treatment choices are often made empirically. Although these drugs are effective, they are difficult to work with, especially in centers that do not have many patients with this disorder. Treatment requires frequent intravenous administration, laboratory monitoring, and careful monitoring for thromboembolic complications.

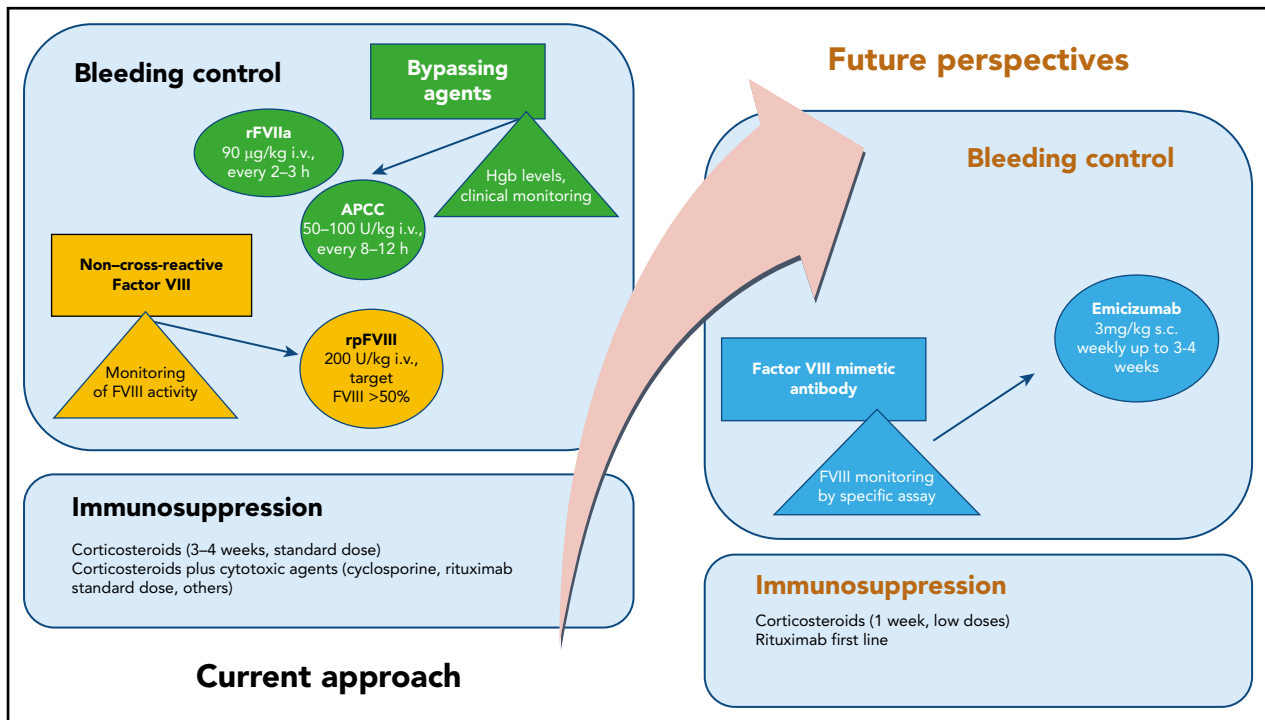
Treatment by eradication (if possible) or suppression of autoantibodies by immunosuppression may lead to complications. Data from international studies have shown that the risk of immunosuppression-related mortality, particularly as a result of infections,

may be greater than the risk of fatal hemorrhages.³

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated FIX and FX to mimic the function of missing activated FVIII. Emicizumab must be administered subcutaneously and is currently approved for prophylaxis in patients with congenital hemophilia A, both with and without inhibitors.⁴

Because of its mechanism of action, emicizumab may be an effective drug for controlling bleeding in patients with AHA. A recent *ex vivo* study⁵ that was performed by adding several concentrations of emicizumab to plasma from patients with AHA, has shown that the drug can restore thrombin generation. The efficacy of emicizumab after APCC or rpFVIII have failed has recently been described in case reports.^{6,7}

The clinical experience now reported by Knoebl et al used an innovative treatment of bleeding control along with reduced-intensity immunosuppression for eradicating inhibitors, which may help overcome the current limits of combined therapy for AHA. This approach, adopted in frail patients, resulted in effective treatment without serious adverse events such as infections or thrombosis. The authors individualized therapy according to clinical



Recommended standard treatment and future perspectives in AHA. hgb, hemoglobin; i.v., intravenous; s.c., subcutaneous.

response and serial laboratory measurements of coagulation FVIII.

Therefore, mimicking FVIII activity to control bleeding in AHA seems to be a promising option (see figure). Laboratory monitoring with FVIII chromogenic assays to taper treatment remains an important limitation to this approach. Other caveats from the report from Kneobl et al are the off-label administration of rituximab combined with low-dose steroids as immunosuppression and the need to avoid concomitant treatment with bypassing agents. In clinical practice, these anti-hemorrhagic agents are administered at the onset of disease or for breakthrough bleeding control. The combination of emicizumab and high-dose APCC has been reported to increase the risk for thrombotic microangiopathy in patients with congenital hemophilia A with inhibitors.⁴

This study raises several intriguing questions: Can emicizumab be administered as first-line or single-agent treatment for bleeding control in AHA? What is the optimal time interval between administration of bypassing agents and administration of emicizumab in AHA to avoid the risk of thrombosis? Does the long

half-life of emicizumab expose patients to long-term adverse effects in the case of breakthrough bleeding control?

The advantages of using emicizumab are the route of administration and the prolonged interval between injections. The study by Kneobl et al further supports the role of using emicizumab, either as first-line treatment or when standard approaches for AHA prove ineffective. However, the clinical role of emicizumab vs other treatment approaches in AHA stills needs to be evaluated in a prospective clinical trial.

Conflict-of-interest disclosure: S.S. acted as consultant for Bayer, BIOFVIIIx, Novo Nordisk, Amgen, Novartis, CSL Behring, and Takeda and received speaker fees from Kedrion, Takeda, Baxalta, CSL Behring, Novo Nordisk, Bayer, Novartis, and Amgen. M.N. acted as consultant for Bayer, BIOFVIIIx, Novo Nordisk, and Amgen and received speaker fees from Kedrion, Octapharma, Baxalta, CSL Behring, Novo Nordisk, and Bayer. ■

REFERENCES

1. Kneobl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. *Blood*. 2021;137(3):410-419.

2. Tiede A, Collins P, Kneobl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. *Haematologica*. 2020;105(7):1791-1801.
3. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. *Blood*. 2015;125(7):1091-1097.
4. European Medicines Agency. Annex I: Summary of Product Characteristics—HEMLIBRA. https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf.
5. Takeyama M, Nogami K, Matsumoto T, Noguchi-Sasaki M, Kitazawa T, Shima M. An anti-factor IXa/factor X bispecific antibody, emicizumab, improves ex vivo coagulant potentials in plasma from patients with acquired hemophilia A. *J Thromb Haemost*. 2020;18(4):825-833.
6. Kneobl P, Sperr WR, Schellongowski P, et al. Emicizumab for the treatment of acquired hemophilia A: lessons learned from 4 very different cases [abstract]. *Blood*. 2018;132(suppl 1). Abstract 2476.
7. Möhnle P, Pekrul I, Spannagl M, Sturm A, Singh D, Dechant C. Emicizumab in the treatment of acquired haemophilia: A case report. *Transfus Med Hemother*. 2019;46(2):121-123.

DOI 10.1182/blood.2020008379

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