It discriminates 4 prognostic subgroups with different 5-year overall survival rates resulting in different treatment implications and combines the parameters TP53 status, IGHV mutational status, serum β2-microglobulin concentration, clinical stage, and age, with different weighting in a prognostic score. The CLL-IPI was initially introduced in 2016 and comprises data of patients who received chemoimmunotherapy.[2]

A plethora of other prognostic scores with focus on different clinical outcome parameters like OS, progression-free survival, or treatment-free survial have been introduced to the field of CLL research, but a meta-analysis by the Cochrane group recently revealed that the CLL-IPI still shows the best discrimination, despite overestimation.[3]

However, the treatment landscape in CLL has dramatically changed in the last years with the introduction of novel oral inhibitors. Against the background of quickly changing treatment possibilities and recommendations, the CLL-IPI might be outdated now. Therefore, several further scores have been introduced to the new treatment landscape.

Soumerai et al[4] developed the first validated risk score to predict OS in patients with relapsed/refractory CLL who were treated with targeted therapies. It identified 4 factors that differ widely from the CLL-IPI including serum β2-microglobulin, lactate dehydrogenase, hemoglobin, and time from initiation of last therapy and helps to identify patients who are at a high risk for early death.

The BALL score identifies a subset of patients with CLL, accounting for about 50% of the whole population, who benefit, in particular, from single agent ibrutinib. It comprises β2-microglobulin, hemoglobin, lactate dehydrogenase, and time elapsed from last therapy <24 months as parameters.[5] However, this score did not show satisfying results in a real-world patient cohort, so the improved survival risk score for ibrutinib, which excludes time to last therapy, was then developed to determine OS in relapsed/refractory patients with CLL treated with ibrutinib.[6]

Furthermore, a 4-factor model consisting of TP53 status, prior treatment, β-2 microglobulin, and lactate dehydrogenase levels was introduced. It identifies patients with an increased risk of ibrutinib failure at treatment initiation and remained significant when applied to either treatment-naive or relapsed/refractory patient cohorts treated with ibrutinib.[7]

In a completely different approach paying tribute to the changing dynamics within the course of the disease, the continuous individualized risk index was evaluated in CLL including the CLL-IPI and minimal residual disease levels. This dynamic risk model seems to be superior to established risk assessment scores in determining clinical outcomes.[8] However, this model is probably too complex to be used broadly in clinical practice but could be a very helpful tool in clinical trials otherwise. Prospectively, an easy-to-use tool will have to be developed for a more individualized management of patients that can be easily implemented into clinical routine and therefore finds broad acceptance. Hence, the CLL-IPI should be reevaluated as soon as more mature data on first-line treatments with oral inhibitors are available.

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REFERENCES

1. Parikh SA, Rabe KG, Kay NE, et al. The CLL International Prognostic Index predicts outcomes in monoclonal B-cell lymphocytosis and Rai 0 CLL. *Blood*. 2021;138(2):149-159.
2. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790.
3. Kreuzberger N, Damen JA, Trivella M, et al. Prognostic models for newly-diagnosed chronic lymphocytic leukaemia in adults: a systematic review and meta-analysis. *Cochrane Database Syst Rev*. 2020;7:CD012022.
4. Soumerai JD, Ni A, Darif M, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. *Lancet Haematol*. 2019;6(7):e366-e374.
5. Molica S, Baumann TS, Lentini M, Levato L, Delgado J, Montserrat E. The BALL prognostic score identifies relapsed/refractory CLL patients who benefit the most from single-agent ibrutinib therapy. *Leuk Res*. 2020;95:106401.
6. Gentile M, Morabito F, Del Poeta G, et al. Survival risk score for real-life relapsed/refractory chronic lymphocytic leukemia patients receiving ibrutinib. A campus CLL study. *Leukemia*. 2021;35(1):235-238.
7. Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: development and validation of a four-factor prognostic model. *J Clin Oncol*. 2021;39(6):576-585.
8. Kurtz DM, Esfahani MS, Scherer F, et al. Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction. *Cell*. 2019;178(3):699-713.

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THROMBOSIS AND HEMOSTASIS

Comment on Silasi et al, page 178

FXII inhibition: multipronged benefits

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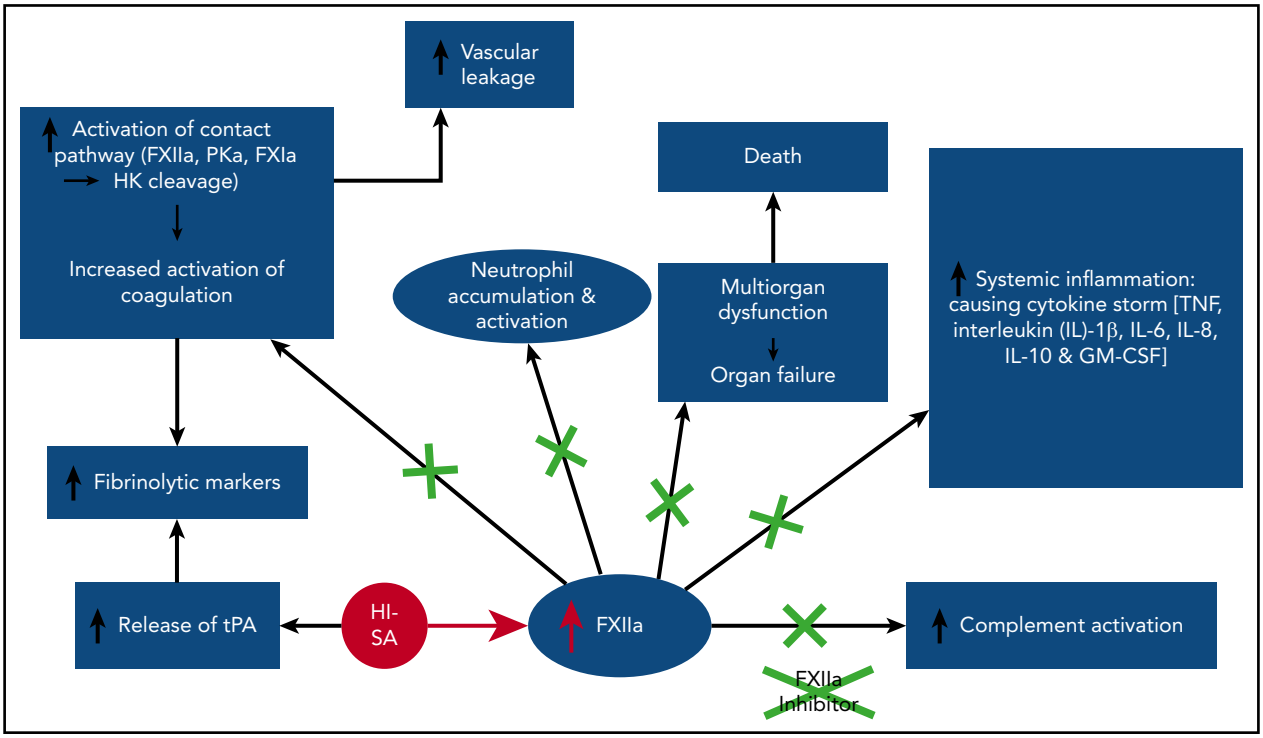
In this issue of *Blood*, Silasi et al[1] identified that inhibition of activated factor XII (FXIIa) using an antibody (5C12) reduces the activation of coagulation and the kallikrein-kininogen pathways, induced by heat-inactivated *Staphylococcus aureus* (HI-SA). Furthermore, by inhibiting FXII function, there was decreased activation of complement and inflammatory cytokines, resulting in preserved organ function and survival of baboons subject to a challenge with HI-SA. These findings suggest potential benefit of prophylactic treatment of patients at increased risk of pathological coagulation and inflammatory responses using an inhibitor of FXIIa. Such indications include prevention of sepsis or its mitigation in severe infections in which FXIIa activity is involved in its pathogenesis.

For many years, the role of FXII in coagulation was not understood, until Renne et al[2] discovered that FXII plays an essential role in the propagation phase of

pathological clot formation while not being required for normal hemostasis. This paradigm shift of a separation between thrombosis and hemostasis led to the concept of anticoagulation using agents with minimal bleeding side effects (ie, the development of inhibitors of FXIIa and FXIa) as next-generation anticoagulants. FXII-deficient individuals do not exhibit a bleeding phenotype and are asymptomatic, whereas FXI deficiency has a mild bleeding phenotype upon a challenge such as trauma or surgery (with the level of bleeding not correlating with FXI levels). Inhibitors of FXIIa and FXIa have shown excellent anticoagulant efficacy with lower bleeding risk than anticoagulants on the market in preclinical models. Less explored is the role FXIIa and FXIa inhibition on the inflammatory pathways. FXII activity leads to increased response of the kallikrein-kinin pathway, resulting in bradykinin release and inflammation.[3,4] In addition, FXIIa is reported to activate the complement pathway.[5] Lupu et al[6] have demonstrated previously that targeting FXI results in decreased coagulation and inflammatory responses using a sepsis baboon model treated with HI-SA. This current manuscript demonstrates that baboons challenged with HI-SA, which were treated an anti-FXII antibody (5C12, which inhibits FXII function), exhibited mild and transient clinical symptoms, recovering fast and reaching the 7-day end point without symptoms. The vehicle-only group did not survive the 7-day study period. The 5C12 FXII inhibitor treatment of the challenged baboons led to reduced reciprocal activation of FXII and prekallikrein, resulting in less high molecular weight kininogen cleavage (indicative of bradykinin release) and downstream activation of coagulation, compared with challenged animals treated with vehicle only. HI-SA challenge in the baboons caused release of tPA and increased levels of plasminogen activator inhibitor-1, as is common in disseminated intravascular coagulation. Elevated markers of fibrinolysis were observed in plasma samples from HI-SA–challenged animals administered vehicle only, but these markers were dramatically reduced in challenged baboons treated with 5C12. HI-SA challenge to the baboons (with vehicle only) led to an early increase in red blood cell and hematocrit, potentially indicative of increased capillary permeability induced by bradykinin generated after high molecular weight kininogen cleavage. This increase was not observed in challenged animals treated with 5C12. Furthermore, striking accumulation of neutrophils was shown in the lungs, evidenced by staining for neutrophil elastase and was accompanied with a marked increase of myeloperoxidase released into the plasma in vehicle only, HI-SA challenged animals, but not those treated with 5C12. This indicates decreased activation of neutrophils associated with inhibition of FXII, which prevented lung pathology at the 7-day end point. HI-SA–challenged baboons with vehicle only had progressive multiorgan dysfunction with organ failure in all animals. These baboons demonstrated signs of early cardiorespiratory distress with a drop in mean systemic arterial pressure, tachycardia, tachypnea, and transient increase of body temperature. Furthermore, these animals gradually developed liver, pancreas, and kidney dysfunction or damage, indicated by elevated serum blood urea nitrogen, creatinine, ALT, and pancreatic



Activation of FXII by heat-inactivated *Staphylococcus aureus* (HI-SA) results in activation of the contact pathway of coagulation leading to kallikrein-triggered generation of bradykinin (resulting in vascular leakage) and downstream activation of coagulation resulting in enhanced fibrinolysis accompanied by the direct release of tPA induced by HI-SA. Elevated FXIIa also results in neutrophil accumulation in the lung and neutrophil activation, alongside multiorgan dysfunction leading to organ failure and mortality. Furthermore, elevated FXIIa directly activates the complement pathway of inflammation and results in a cytokine storm of elevated systemic markers of inflammation. Inhibition of all these activities of FXIIa using 5C12 attenuates all these pathways resulting in improved outcomes in this model of HI-SA–induced sepsis. GM-CSF, granulocyte-macrophage colony stimulating factor.

amylase. After an initial increase in blood glucose at 2 hours, animals became hypoglycemic within 4 to 8 hours post-challenge, indicative of metabolic disturbance. In contrast, 5C12 treatment prevented the drop in blood pressure and rise in body temperature. The treated animals were protected from acute organ damage, and hypoglycemia was less severe. In addition, untreated SI-HA–challenged baboons had highly elevated levels of circulating nucleosomes (a marker of cell death). Inhibition of FXIIa significantly reduced plasma nucleosomes, consistent with organ preservation.

Baboons subjected to HI-SA without 5C12 demonstrated increased complement activation, evidenced by elevated circulating C3b and soluble terminal complement complex C5b-9. Inhibition of FXII with 5C12 resulted in markedly reduced C3b and sC5b-9. HI-SA challenge in baboons with vehicle only provoked systemic inflammation evidenced by high levels of plasma cytokines, including tumor necrosis factor; interleukin-1β (IL-1β), IL-6, IL-8, IL-10; and granulocyte-macrophage colony stimulating factor. This cytokine storm was reduced when the HI-SA–challenged animals were treated with 5C12.

These exciting data show promise for reduced inflammation and coagulation with prophylactic treatment using an FXIIa inhibitor. Although the 2 studies are not directly comparable, the effects of FXII inhibition in the same animal model showed equivalent positive effects on reducing activation of coagulation but with apparent stronger effects on reducing inflammatory biomarkers than prophylactic FXI inhibition[6] (although other factors such as dosage/potency would need to be taken into consideration as potential limitations of such a direct comparison).

To summarize, inhibition of FXIIa activity in HI-SA–treated baboons prevented the activation of kallikrein-kininogen and coagulation systems, decreased complement activation and inflammatory cytokines, and preserved organ function, leading to survival of the baboons against the HI-SA challenge (see figure). The Silasi et al article demonstrates potential of FXII inhibition beyond its antithrombotic properties but also anti-inflammatory benefits that may apply to many clinical indications beyond the model described. Interestingly, another company (CSL Behring) has also developed an antibody targeting FXIIa (garadacimab or CSL312), which has shown promise in the treatment of patients with hereditary angioedema.[7] A phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate CSL312 in coronavirus disease 2019 has just been completed.[8] It will be interesting to see the data from this study. The future is very exciting with the potential of employing FXIIa inhibitors prophylactically, for both anticoagulant and anti-inflammatory efficacy with minimal bleeding side effects.

Conflict-of-interest disclosure: The author is a founder of LUNAC Therapeutics, which develops small molecule FXIIa inhibitors. ■

REFERENCES

1. Silasi R, Keshari RS, Regmi G, et al. Factor XII plays a pathogenic role in organ failure and death in baboons challenged with *Staphylococcus aureus*. *Blood*. 2021;138(2):178-189.
2. Renné T, Pozgajová M, Grüner S, et al. Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med*. 2005;202(2):271-281.
3. Tankersley DL, Finlayson JS. Kinetics of activation and autoactivation of human factor XII. *Biochemistry*. 1984;23(2):273-279.
4. Tayeh MA, Olson ST, Shore JD. Surface-induced alterations in the kinetic pathway for cleavage of human high molecular weight kininogen by plasma kallikrein. *J Biol Chem*. 1994;269(23):16318-16325.
5. Ghebrehiwet B, Randazzo BP, Dunn JT, Silverberg M, Kaplan AP. Mechanisms of activation of the classical pathway of complement by Hageman factor fragment. *J Clin Invest*. 1983;71(5):1450-1456.
6. Silasi R, Keshari RS, Lupu C, et al.. Inhibition of contact-mediated activation of factor XI protects baboons against *S aureus*-induced organ damage and death [published correction appears in *Blood Adv*. 2019;3(4):658-669]. *Blood Adv*. 2019;3(4):658-669.
7. HAE International. Results for garadacimab as preventive HAE treatment. https://haei.org/results-for-garadacimab-as-preventive-hae-treatment/. Accessed 22 February 2021.
8. Clinicaltrials.gov. Treatment with CSL312 in adults with coronavirus disease 2019 (COVID-19). https://clinicaltrials.gov/ct2/show/record/NCT04409509?term=Garadacimab&draw=2&rank=2. Accessed 22 February 2021.

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THROMBOSIS AND HEMOSTASIS

Comment on Whitworth et al, page 190

Thrombosis with COVID-19: kids get it too

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In this issue of *Blood*, Whitworth et al provide much needed data on thrombosis rates and risk in pediatric patients with coronavirus disease 2019 (COVID-19).[1]

Thrombotic events (TEs) are a frequent complication in hospitalized adults with severe COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[2] Although much has been learned about TE rates and risks in adults, relatively little is known about this problem in the pediatric population. The overall incidence of COVID-19 and thrombosis is markedly lower in children, which has added challenges to studying this condition in this age group. In addition, children and adolescents are uniquely affected by a postinfectious hyperinflammatory syndrome after SARS-CoV-2 infection, termed multisystem inflammatory syndrome in children (MIS-C).[3] Patients with MIS-C are also at risk for thrombosis. Given the paucity of high-quality evidence in this age group, pediatric providers have relied heavily on data extrapolated from adult studies and expert opinion for pediatric-specific guidance to manage thrombotic risk.[4] The results of the study in this issue provide important information to help fill the knowledge gap in this population.

Whitworth et al describe the risks and rates of thrombosis in a multicenter