

Comment on Ansell et al, page 115

# Ciraparantag: the next anticoagulant airbag?

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**In this issue of *Blood*, Ansell et al summarize the mechanism of action, pharmacokinetics, and pharmacodynamics of ciraparantag, a small molecule under development as an anticoagulant reversal agent.<sup>1</sup>**

Direct oral anticoagulants (DOACs) revolutionized oral anticoagulation. Among other favorable characteristics, the most compelling advantage of DOACs over warfarin is a reduced risk of serious bleeding. Owing to their short half-lives, temporary discontinuation of DOACs alone may be sufficient for many instances of bleeding, or semiurgent or low-bleed-risk invasive procedures. However, emergencies such as major bleeding carry substantial short-term mortality (up to 14% within 30 days), emphasizing the need for agents that improve clinical outcomes by normalizing hemostasis rapidly and effectively.<sup>2</sup>

Ciraparantag binds to heparins and the DOACs through noncovalent charge-charge interactions. Binding to other drugs and blood proteins (including coagulation factors) has not been demonstrated. Studies in human volunteer subjects receiving 15 to 300 mg of ciraparantag showed dose-proportional pharmacokinetics with maximum serum concentrations achieved within 5 to 9 minutes and half-life of 12 to 19 minutes.<sup>3</sup> Ciraparantag is hydrolyzed by serum peptidases into nonactive metabolites and is renally excreted. In animal bleeding models, ciraparantag reduced blood loss after tail transection in rats treated with edoxaban, dabigatran, apixaban, rivaroxaban, unfractionated heparin, and enoxaparin. Similarly, ciraparantag (at doses of 20 mg/kg and 30 mg/kg) reduced bleeding time following liver laceration in edoxaban-treated rats. Within 60 minutes of ciraparantag administration, fibrin strands were seen in blood pellets examined by electron microscopy. In a randomized double-blind trial, human volunteer subjects were treated with edoxaban (60 mg oral dose) followed by ciraparantag (100 to 300 mg) or placebo.<sup>4</sup> Ciraparantag rapidly (within 10 to 30 minutes) corrected prolonged whole blood clotting time (WBCT)

from 37% above baseline to 10% above baseline, an effect that lasted for 24 hours. Adverse events were mild with no evidence of procoagulant activity. Similar findings were seen after administration of ciraparantag (100 to 300 mg) or placebo in healthy volunteer subjects treated with enoxaparin (1.5 mg/kg). There was no difference in WBCT between the ciraparantag and placebo groups at 12 to 15 hours after administration, consistent with anticoagulant clearance.

The findings summarized by Ansell and colleagues, including rapid onset of action, reduction in bleeding in animal models, prolonged pharmacodynamic effects, and tolerability, support the potential of ciraparantag as an anticoagulant reversal agent. Similar to the clinical development of other anticoagulant reversal agents idarucizumab (for dabigatran) and andexanet alfa (for factor Xa inhibitors), there are important considerations for designing and conducting clinical trials to establish the efficacy and safety of reversal agents.

The challenges of measuring DOAC drug levels and interpreting their clinical significance in patients being considered for urgent reversal are well described.<sup>2</sup> Routine coagulation tests are not accurate or reliable for determining DOAC levels, and specific DOAC assays are not widely available. Furthermore, there are no established DOAC therapeutic ranges, and the plasma concentrations corresponding to a clinically significant hemostatic defect are unknown. As a result, decisions to administer reversal agents are often made using the timing of the last dose to inform the likelihood of clinically significant drug levels. For example, in the ANNEXA-4 study, which evaluated andexanet alfa, patients with acute major

bleeding on factor Xa inhibitors were eligible if the last dose was within the previous 18 hours<sup>5</sup>; drug levels were below the cutoff for inclusion in the efficacy analysis in up to 25% of patients, suggesting they may not have had clinically significant anticoagulant levels, although the threshold for "clinically significant" is uncertain. This has important implications for determining net clinical benefit for individual patients, and for health care resource utilization and costs. An additional complexity of laboratory testing with ciraparantag is its binding to anionic additives in blood collection tubes (eg, sodium citrate, EDTA) precluding the use of routine coagulation tests until it is cleared. As a result of this characteristic, the WBCT was used for laboratory assessment of anticoagulant effect in animal models and human volunteer studies. Although validated for use in these research studies, this test is not routinely available for clinical use, requires expertise, and may be subject to interobserver variability.

Ultimately, the efficacy and safety of reversal agents can only be established with randomized trials measuring clinically relevant patient-important outcomes. There is uncertainty regarding the incremental benefits and harms of idarucizumab and andexanet alfa, which were studied in open-label prospective cohort studies lacking control groups.<sup>5,6</sup> Cohort studies evaluating 4-factor prothrombin complex concentrate (4-factor PCC) in patients with bleeding on factor Xa inhibitors similarly lacked control groups.<sup>7</sup> The ANNEXA-I randomized controlled trial is evaluating andexanet alfa vs usual care for intracranial hemorrhage in patients receiving factor Xa inhibitors (#NCT03661528). Although the results of ANNEXA-I are highly anticipated, the role of reversal remains uncertain in patients with gastrointestinal bleeding, the most frequent single site of bleeding. Among patients with major gastrointestinal bleeding in REVERSE-AD and ANNEXA-4, the 30-day mortality rate was 11%.<sup>8,9</sup>

Another important consideration is the reliable measurement of bleeding cessation. Ascertainment of outcomes defined using subjective criteria is vulnerable to bias. In REVERSE-AD, clinical hemostatic efficacy was assessed by treating physicians, whereas in ANNEXA-4 it was assessed by independent adjudicators using prespecified definitions.<sup>5</sup> To

standardize outcome ascertainment and reporting, the International Society on Thrombosis and Haemostasis published consensus definitions of hemostatic efficacy.<sup>10</sup> Importantly, various definitions of hemostatic efficacy have not been prospectively validated.

In REVERSE-AD, ANNEXA-4, and 4-factor PCC studies, high 30-day mortality rates were seen after major bleeding (13% to 32%) despite moderate to high rates of clinical hemostasis, which is not entirely explained by index bleed site.<sup>5,6</sup> These findings suggest that existing definitions of hemostatic efficacy may not adequately capture ongoing bleeding, or that major bleeding triggers a series of adverse events leading to death despite cessation of bleeding. In addition to concerns about thrombotic events after anticoagulant reversal, these findings raise additional uncertainty about overall net clinical benefit. The results of clinical trials designed to establish the effect of anticoagulant reversal agents (including ciraparantag) on clinically relevant and patient-important outcomes are eagerly awaited.

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## TRANSPLANTATION

Comment on Assmann et al, page 126

# From the inside: GVHD and glucose metabolism

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**In this issue of *Blood*, Assmann et al show that elevated glycolysis is a traceable metabolic feature of infiltrating T cells, particularly in the early phase of graft-versus-host disease (GVHD).<sup>1</sup> This observation verifies that noninvasive imaging of the metabolic activity of T cells can visualize dynamic inflammatory processes in patients after allogeneic hematopoietic stem cell transplantation (HSCT). Over the past 10 to 20 years, several new approaches, either tested in prospective randomized studies (eg, studies aiming to optimize the conditioning therapy prior transplantation) or evaluated by analyzing large clinical data sets (eg, retrospective studies exploring the impact of better HLA-matching between donor and patients) have led to improved survival outcomes in patients treated with HSCT.<sup>2-4</sup> In addition to these clinical data, experimental research has helped to elucidate the underlying immunological processes. In particular, the better understanding of T-cell biology has recently led to the successful development of novel treatment strategies for the most relevant complication after allogeneic HSCT, GVHD.<sup>5</sup> Despite these advances, GVHD still affects 30% to 60% of patients after allogeneic HSCT.<sup>6</sup> Although the diagnosis of GVHD of the skin can be easily established visually in most cases, GVHD of the intestine or liver is still defined by surrogate parameters like stool volume or increased bilirubin, which are nonspecific and have limited value in establishing the diagnosis of GVHD, or prediction of response to treatment or outcome.<sup>7,8</sup>**

By visualizing enhanced glycolysis of alloreactive T cells by metabolic magnetic resonance imaging (MRI), Assmann et al were able to detect the onset of GVHD even before clinical manifestation in a chronic GVHD animal model. Further detailed analysis of the experimental GVHD model and data from single-cell sequencing of patient-derived circulating T cells corroborated their hypothesis that increased glycolysis is a feature in the early activation and organ infiltration (liver) of alloreactive T cells causing GVHD.

Interestingly, peak metabolic activity (as measured by metabolic MRI using hyperpolarized pyruvate) preceded the clinical symptoms of GVHD. At later time points during the course of GVHD, the differences compared with syngeneic controls were less prominent, probably due to the limited target region analyzed and/or diminished T-cell activity.

Today, in vivo imaging of metabolic activity using positron emission tomography (PET) with fluorodeoxyglucose (FDG) or