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XIX Convegno Triennale sugli Aspetti Clinici e Sociali dell'Emofilia ABSTRACT N. CO-28

2.01 Hemophilia - clinical and treatment issues

SYNERGISTIC EFFECT OF RECOMBINANT FACTOR INFUSION ON THROMBIN GENERATION IN HEMOPHILIA PATIENTS UNDER EMICIZUMAB OR CONCIZUMAB PROPHYLAXIS

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Background and Aims. Hemophilia is caused by deficiency of factor VIII (FVIII) or IX (FIX). Current prophylactic strategies include non-replacement therapies such as emicizumab (emz) and concizumab (cncz), both capable of enhancing thrombin generation (TG) parameters. Nevertheless, breakthrough bleeding and surgical procedures remain challenging clinical settings, often requiring concomitant administration of recombinant clotting factors. This study aimed to evaluate the impact of recombinant factor infusion on TG profiles in patients receiving emz or cncz prophylaxis.

Materials and Methods. Twenty-three patients (pts) were screened: 21 receiving emz and 2 cncz within the Novo Nordisk study NCT04082429. Only 4 pts required recombinant factor replacement for surgery or breakthrough bleeding and were included in the analysis. The emz group comprised 3 pts with hemophilia A (1 moderate-severe, 2 severe), treated for major surgery (n=2) or bleeding (n=1). The cncz group included 1 pt with severe hemophilia B evaluated during three separate bleeding episodes requiring FIX infusion. Blood samples were collected within 12 hours after recombinant factor infusion. TG was performed in platelet-poor plasma using the ST Genesia® system (Stago, Asnières-sur-Seine, France) with STG BleedScreen reagent. Baseline TGA values were obtained from previously stored follow-up samples collected during prophylaxis with the non-replacement therapy alone.

Results. Following factor infusion, TG changes were heterogeneous in the emz group (Table 1). Pts 2 and 3 showed the expected procoagulant response, whereas Pt 1 displayed a paradoxical reduction in TG parameters together with StartTail prolongation. Despite achieving a post-infusion FVIII plasma level of 29%, Pt 1 showed lower thrombin generation potential compared with baseline. In the cncz-treated pt, all three bleeding episodes showed a consistent pattern characterized by increased Peak Height associated with reduced ETP and StartTail values.

Conclusions. Distinct TG kinetic profiles emerged between the two non-replacement therapies. Cncz was associated with an early thrombin burst followed by rapid degradation, whereas emz produced a more gradual TG curve, consistent with its mechanism of action. The paradoxical reduction in TG observed in Pt 1 despite adequate FVIII levels may reflect clinical factors such as increased perioperative clotting factor consumption and concomitant heparin administration, both potentially limiting TG. These findings support the role of TG as a comprehensive global assay for individualized management of prophylaxis, bleeding, and surgery in hemophilia. Future application of TGA in platelet-rich plasma may further improve physiological assessment by incorporating cellular interactions occurring in vivo.

	Emicizumab			Concizumab		
	Patient 1	Patient 2	Patient 3	Patient 4 - bleeding 1	Patient 4 - bleeding 2	Patient 4 - bleeding 3
Peak Height (nM)	-37.7	+29.9	+67.8	+11.3	+23.9	+12.2
ETP (nM.min)	-25.9	+5.7	+11.1	-8.4	-2.5	-1
Start Tail (min)	+27.1	-12.4	-27.3	-16.1	-15.2	-10.4
Total dose of recombinant factor	30 IU/Kg	50 IU/Kg	30 IU/Kg	30 IU/Kg	30 IU/Kg	30 IU/Kg
Factor level after infusion (chromogenic assay)	29.2%	38.7%	19.3%	12.2%	9%	6.6%

Table 1