台灣血栓暨止血學會
Taiwan Society of Thrombosis and Hemostasis

113年度第一次學術研討會

2024 TSTH 1st Regular Academic Meeting

台灣血栓暨止血學會

Taiwan Society of Thrombosis Hemostasis

March 16, 2024
臺大醫院兒童醫療大樓地下一樓講堂
National Taiwan University
Children's Hospital

台灣血栓暨止血學會 113 年度第一次學術研討會
2024 TSTH 1st Regular Academic Meeting

時間：113 年 03 月 16 日 (週六) 13:00~17:00
地點：臺大醫院兒童醫療大樓地下一樓講堂 (中山南路 8 號)
大會主席：邱世欣 理事長

時間	題目	演講者
12:50~13:10	註冊	‘
13:10~13:15	開幕致詞	邱世欣 理事長
13:15~13:20		Moderator：徐會棋 醫師
13:20~13:35	Platelet activation and cytokine release of interleukin-8 and interferon-gamma-induced protein 10 after ChAdOx1 nCoV-19 coronavirus vaccine injection	吳懿峰 醫師 花蓮慈濟醫院
13:35~13:45	討論	
13:50~14:05	Beyond Standard Diagnosis: Whole Genome Sequencing Reveals a Unique Case of von Willebrand Disease in Siblings	翁德甫 醫師 中山附醫
14:05~14:15	討論	
14:20~14:35	Successful Survival with Intracranial Hemorrhage after Resuscitation and Emergent Percutaneous Coronary Intervention from Out-of-Hospital Cardiac Arrest in a Patient with Hemophilia A: One Case Report	黃彥閔 醫師 基隆長庚醫院
14:35~14:45	討論	
14:45~15:10	Coffee Break	
15:10~15:15		Moderator：王建得 醫師
15:15~15:30	Severe hemophilia B associated with X inactivation in a female carrier of a known factor IX gene mutation	林佩瑾 醫師 高醫附醫
15:30~15:40	討論	
15:45~16:00	External Validation and Clinical Application of Prediction Models for rFVIIIFc Half Life in People with Hemophilia A on rFVIIIFc Prophylaxis Therapy	張家堯 醫師 北醫附醫
16:00~16:10	討論	
16:15~16:30	Bone health of hemophilia A patients using emicizumab	周聖傑 醫師 台大醫院
16:30~16:45	討論	
16:45~16:50	閉幕致詞	沈銘鏡榮譽理事長

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專科證書
內科專科醫師證書
血液病專科醫師證書
血液及骨髓移植專科醫師證書
台灣臨床腫瘤專科醫師證書

專科學會
台灣內科學會、中華民國血液病學會、中華民國血液及骨髓移植學會、中華民國癌症醫學會、台灣臨床腫瘤學會、中華民國血友病協會

著 作

1. 吳懿峰 , 沈銘鏡 , 張正雄 : 骨髓增生性疾病的基因學與臨床探討 Biomedicine 生物醫學 2008; 1: 190-197
2. YF Wu, CS Chang, CY Chung, HY Lin, CC Wang, MC Shen. Superwarfarin intoxication: hematuria is a major clinical manifestation. Int J Hematol (2009)90:170-173

Platelet activation and cytokine release of interleukin-8 and interferon-gamma-induced protein 10 after ChAdOx1 nCoV-19 coronavirus vaccine injection

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關鍵詞
冠狀病毒疫苗 , 白血球介素 , 干擾素誘導蛋白 , 血小板活化 , 細胞因子

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Keywords
nCoV-19 coronavirus, vaccine, ChAdOx1, platelet activation, platelet factor 4, cytokine release

Coronavirus disease 2019 COVID-19 vaccines are associated with serious thromboembolic or thrombocytopenic events, including vaccine-induced immune thrombocytopenia and thrombosis and immune thrombocytopenia, particularly AZD1222/ChAdOx1. According to the proposed mechanism, COVID-19 vaccines stimulate inflammation and platelet activation.

In this study, we analyzed the role of AZD1222/ChAdOx1 vaccines in the activation of platelets and the release of anti-PF4 antibodies and inflammatory cytokines in a cohort of healthy donors without vac-cine-induced immune thrombotic thrombocytopenia VITT. Forty-eight healthy volunteers were enrolled in this study. Blood samples were collected from peripheral blood at three time points: before vaccination and 1 and 7 days after vaccination. Compared with prevaccination data, a decrease in leukocyte and platelet counts was observed 1 day after vaccination, which recovered 7 days after injection. The percentage of activated GPIIb/IIIa complex PAC-1 under high ADP or thrombin receptor-activating peptide stimulation increased 1 day after vaccination. Furthermore, interluekin-8 IL-8 and interferon-gamma-induced protein 10 IP-10 increased significantly. Additionally, platelet activation and inflammation, with the release of cytokines, were observed however, none of the individuals developed VITT. Mild thrombocytopenia with platelet activation and inflammation with an elevation of IL-8 and IP-10 were observed after AZ vaccination.

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兒童癌症（血液癌症與各種實體腫瘤）
兒童血管瘤及其他良性腫瘤
兒童骨髓移植及併發症（排斥、感染）治療

Beyond Standard Diagnosis: Whole Genome Sequencing Reveals a Unique Case of von Willebrand Disease in Siblings

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Background

Von Willebrand Disease (VWD) is a hereditary bleeding disorder, characterized by a qualitative or quantitative deficiency of von Willebrand factor (VWF), a crucial component in the blood coagulation process. The phenotypic diversity and genetic heterogeneity of VWD pose significant challenges in diagnosis and management. This study presents a unique case of two siblings diagnosed with VWD, showcasing atypical clinical manifestations. Initially categorized under the broad umbrella of VWD, their distinct bleeding patterns and severity hinted at a more complex genetic background.

Methods

A patient presented at my clinic with a history of prolonged bleeding post-sinus surgery and dental procedures, but without significant joint disease. Laboratory tests revealed Factor VIII levels at 6.5 IU/dL, VWF antigen (VWF:Ag) at 16.8 IU/dL, and VWF activity to glycoprotein Ib receptor (VWF:GP1bM) at 23 IU/dL. His younger brother exhibited similar symptoms, including extended bleeding following minor procedures and hematoma formation post-exercise. His tests showed Factor VIII at 4.2 IU/dL, VWF:Ag at 13.1 IU/dL, and VWF:GP1bM at 18.6 IU/dL. In contrast, their parents and younger sister demonstrated normal levels of Factor VIII, VWF:Ag, and VWF:GP1bM. The response to the DDAVP test in both brothers indicated a transient increase in VWF:Ag, GP1bR, and Factor VIII.

Given these unusual presentations and laboratory findings, standard diagnostic tests were insufficient to accurately diagnose the brothers' condition. Consequently, we resorted to Whole Genome Sequencing (WGS) for a definitive diagnosis.

Results

WGS analysis ruled out any genetic mutations in Factor VIII. However, the sequencing results for von Willebrand Disease (VWD) revealed a combination of heterozygous mutations: c.3674+1G>T and c.2574C>G. The c.3674+1G>T mutation is known to be associated with the recessive genotype of Type 3 VWD, while c.2574C>G is linked to Type 1 VWD.

Subsequent investigations confirmed that each parent carried one of these mutations. The father possessed the c.3674+1G>T mutation, commonly associated with Type 3 VWD, and the mother carried the c.2574C>G mutation, indicative of Type 1 VWD. This genetic makeup explained the unique clinical presentation and laboratory findings in their sons.

Conclusions

The findings of this study underscore the complexity and variability of VWD, particularly in cases where conventional diagnostic methods fall short. The co-occurrence of Type 1 and Type 3 VWD in the same family, elucidated through Whole Genome Sequencing, highlights the potential for atypical genetic combinations in hereditary bleeding disorders. This revelation not only challenges the traditional classification of VWD but also emphasizes the need for comprehensive genetic analysis in ambiguous cases.

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Successful Survival with Intracranial Hemorrhage after Resuscitation and Emergent Percutaneous Coronary Intervention from Out-of-Hospital Cardiac Arrest in a Patient with Hemophilia A: One Case Report

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關鍵詞
A 型血友病 , 急性冠心症 , 經皮冠心動脈介入術 . 心肺復甦術 , 到院前心跳停止 (OHCA), 顱內出血

Yen-Min Huang[1,2,3] , Chieh-Ping Wen[3], Hsuan-Ching Lin[4], Jia-Ruey Tsai[5,6], Shu-Hsia Hu[6], Chia-Yau Chang[6,7,8]
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Keywords
Hemophilia A, Acute coronary syndrome, Percutaneous coronary intervention, Resuscitation, Out-of-Hospital Cardiac Arrest, Intracranial hemorrhage

Introduction

As great advance in hemophilia care and increase in life expectancy of people with hemophilia (PWH), age-related co-morbidity, such as acute coronary syndrome (ACS) in PWH has become not uncommon. However, sudden death due to ACS in PWH is not common.

Materials & Methods

We reviewed and reported the chart of one patient with severe hemophilia A, who suffered from sudden collapse due to ACS and came alive after resuscitation. The intracranial hemorrhage after catheterization complicated his condition, with post-resuscitation hypoxia ischemic encephalopathy.

Results

A 52-year-old male non-inhibitor patient with severe-type hemophilia A had received long-term on-demand therapy. He had ever suffered from traumatic fracture of right distal femur, status post surgery in 2011, and twice episodes of intramural hemorrhage (IMH) of small intestine in 2019. After that (recovery from IMH), he started to receive prophylaxis therapy with rFVIIIFc 65 iu/kg once weekly, with trough levels of 2%. His cardiovascular risks (CV) included obesity, smoking, VWF:Ag levels 130%.

Unfortunately, in 2023, he suffered from sudden collapse for near 15 min, then resuscitation was started by emergency medical technician on the ambulance for around 30 min. Then resuscitation was kept at ER of Hospital for 30 min, when no one knew he was a patient with severe Hemophilia A. He had return of spontaneous circulation and EKG revealed ST segment elevation. He was sent for emergent percutaneous coronary intervention (PCI), without clotting factor replacement before PCI. One bare mental stent was implanted in left circumflex coronary artery due to total occlusion with thrombus in situ. However, after successful stent implantation, intracranial hemorrhage (ICH) occurred. Therefore, after hemophilia A in him was identified, factor VIII (FVIII) replacement with intensive care were started. Under aggressive replacement of FVIII, his ICH was gradually resolved, with physiotherapy; but post-resuscitation hypoxia ischemic encephalopathy gradually developed. Although marked neurological sequalae were left.

Conclusion

PWH with high CV risks should be identified early. PCI in PWH exists bleeding risk due to dual anti-platelet therapy with heparin. Therefore, adequate clotting factor replacement should be given to avoid bleedings. Good identification of PWH could prevent from delayed replacement therapy.

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Severe hemophilia B associated with X inactivation in a female carrier of a known factor IX gene mutation

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Keywords
haemophilia, symptomatic female carrier, skewed X chromosome inactivation, int22h-1/int22h-2-flanked Xq28 deletion

Purpose

Female carriers with hemophilia B rarely have a severe phenotype because hemohilia B is an X-linked recessive bleeding disorder. Here, we reported a five-year-old girl with severely affected hemophilia B with frequent muscular and joint bleeds noted since she was 1years and 7 months old. She has a family history of hemophilia B. Isolated severe factor IX deficiency (1~2%, normal range 50~150%) without IX inhibitor was noted. On-demand factor IX replacement therapy was administered frequently and switched to prophylaxis treatment at the age of 3. Annual bleed rate reduced from 18 to 3.5 after prophylaxis treatment started.

Methods

DNA sequencing was used to detect factor IX mutations. Cytogenetics studies including traditional giemsa banding and array-based comparative genomic hybridization (aCGH) were performed to detect chromosome abnormalies. Human androgen receptor (HUMARA) assay was used to explore the X chromosome inactivation (XCI) pattern. Finally, we performed whole exome sequencing (WES) to find if there are causative variants or copy number variations.

Results

Heterozygous splicing substitution in intron 3 (c.277+1 G>T) of the factor IX gene was detected in this patient and her mother. Chromosome giemsa banding showed 46 XX and aCGH of this patient revealed a heterozygous 441kb deletion in Xq28 region which flanked int22h-1/int22h-2. HUMARA assay found that the paternal X chromosome was extremely skewed inactivation. WES also showed a heterozygous copy number variation (CNV) loss of 449.4kb in the Xq28 region flanked int22h-1/int22h-2. Multiplex Ligation-dependent Probe Amplification (MLPA) of factor VIII gene, of which the exon1-22 is located in the Xq28 deleted region, was performed in the patient and her parents. A heterozygous exon 1-22 deletion of factor VIII gene was only found for this patient and no deletion was found for her parents. Therefore, a de novo int22h-1/int22h-2-flanked Xq28 deletion associated skewed X‐inactivation was concluded to cause the severe phenotype for this female hemophilia B carrier.

Conclusion

This patient inherited a heterozygous splicing substitution of the factor IX gene from the mother, a typical female hemophilia B carrier, and suffered from severe phenotype due to an additional de novo int22h-1/int22h-2-flanked Xq28 deletion in the paternal X chromosome, which resulted in parternal X chromosome inactivation. Our approaches successfully explored the molecular evidences of the rare phenotype and helped the family for hereditary consultation for their future offsprings.

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東亞血友病論壇 (EAHF) 口頭發表：旅行獎 (2015 日本東京)
國際血栓止血學會大會 (ISTH congress) 口頭發表：世界展望獎 (2017 德國柏林)
亞太血栓止血學會大會 (APSTH) 口頭報告：研究論文獎 (2021 韓國光州線上會議)

External Validation and Clinical Application of Prediction Models for rFVIIIFc Half Life in People with Hemophilia A on rFVIIIFc Prophylaxis Therapy

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關鍵詞
A 型血友病 ,rFVIIIFc 半衰期 , 預測模式 , 外部驗證 , 藥物動力學

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Hemophilia A, rFVIIIFc Half Life, Prediction Models, External validation, pharmacokinetics

Introduction

The half life of rFVIIIFc for people with hemophilia A (PwHA) varies greatly. Understanding the factors influencing the variation and assessment of rFVIIIFc half life is important for personalized treatment.

Methods

Eighty-five severe-type PwHA on rFVIIIFc prophylaxis therapy receiving an evaluation of half life by the Web-Accessible Population Pharmacokinetic (PK) Service—Hemophilia during 2019–2021 were retrospectively enrolled. The 50-patient PK profiles before 2021 were used for analysis and developing prediction models of half life, and the 35-patient PK profiles in 2021 were used for external validation.

Results

The patients in the development cohort were aged 8–64, with a median rFVIII-Fc half life of 20.75h (range,8.25–41.5h). There was no significant difference between the development cohort and validation cohort in age, BMI, baseline VWF levels, positive inhibitors history and HCV infection, except ratio of patients with O blood type. By multivariate linear regression analysis, we found many predictors of rFVIII-Fc half life and the three prediction equations of rFVIIIFc half life(T) were respectively developed as T for non-O group patients= 0.81+0.63 (BMI,kg/m2) +6.07 (baseline VWF:Ag, IU/mL), T for O group patients= 0.68+13.30 (baseline VWF:Ag,IU/mL) +0.27 (BW,kg) 1.17 (BMI,kg/m2) +16.02 (VWF:activity/VWF:Ag ratio), and T for overall patients= 1.76 + 7.24 (baseline VWF:Ag,IU/mL) — 3.84 (Inhibitor history) +2.99 (HCV infection) — 2.83 (O blood group) +0.30 (Hct,%), which explained 51.97%, 75.17%, and 66.38% of the half life variability, respectively. For internal validation, there was a significant correlation between the predicted and observed half lives. For external validation, there was also a significant correlation between the predicted and observed half lives in the validation cohort. The median half life deviation was +1.53h, +1.28h, and +1.79h for the equations of non-O group, O group, and overall group patients, respectively.

Conclusion

Prediction equations of rFVIIIFc half life were developed for the non-O and O blood groups and overall PwHA with a good degree of external validation. The external validation is important for clinical application to real world. Out prediction equations here can be applied to patients aged 8–64 without the need for PK blood sampling and clinically valuable for personalized therapy.

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TSTH Highlights of ASH 2023 Post-ASH

Bone health of hemophilia A patients using emicizumab

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Background

Hemophilia patients have been observed to exhibit a higher prevalence of osteoporosis compared to age-matched general population. However, the underlying mechanism responsible for this association remains poorly understood. One hypothesis proposes that factor VIII itself may possess additional physiological functions that contribute to bone health. Conversely, alternative viewpoints suggest that overall coagulation function or thrombin generation may play a pivotal role in maintaining optimal bone health. The introduction of emicizumab, a bispecific antibody that mimics the coagulation function of factor VIII but possesses a structurally distinct composition, presents an opportunity to shed light on this matter. Therefore, the primary objective of this study is to explore and compare the bone health status of hemophilia patients, distinguishing between those utilizing emicizumab and those who are emicizumab-naïve.

Method

From June 2019 to June 2023, at the hemophilia center of National Taiwan University Hospital, additional examinations to assess the patients' bone health were performed with routine annual joint health evaluations for patients with hemophilia A (PwHA) and B (PwHB). This included the use of dual-energy X-ray absorptiometry scan (DEXA) to measure the bone mineral density (BMD) of the lumbar spine, hip, and femur. Furthermore, the serum levels of procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide (CTX) were measured as reference markers for bone formation and bone resorption, respectively. The Kruskal-Wallis test was utilized to statistically evaluate the observations among the three groups.

Results

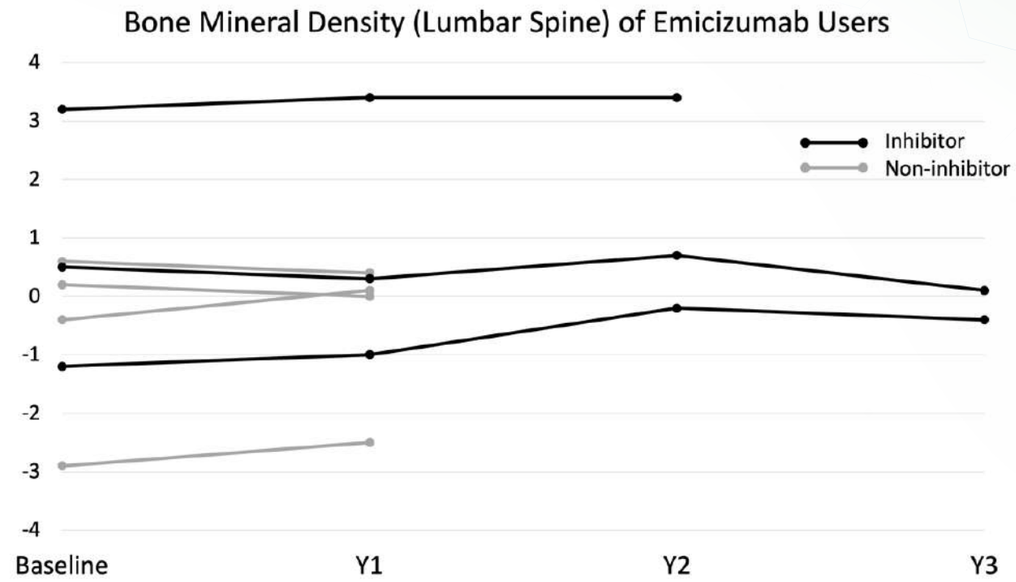
The study population was divided into three distinct groups based on their hemophilia subtype and treatment: PwHA who had been utilizing emicizumab for more than one year (n=8), PwHA individuals receiving regular factor VIII treatment (n=16), and PwHB (n=10). The analysis of the collected data, as presented in the accompanying table, revealed that the three groups exhibited similar characteristics in terms of age, annual bleeding rate, and joint conditions. Moreover, no statistically significant differences were detected in the measurements of bone mineral densities (BMDs) and biomarkers. However, it is worth noting that there appeared to be a potential trend toward higher levels of P1NP in the PwHB group.

In the case of PwHA patients using emicizumab, we examined the longitudinal changes in T-score of BMD over time. Notably, three PwHA patients with baseline T-scores below zero demonstrated improvements in their T-scores after one year of emicizumab treatment.

Conclusion

The results of this study indicate a lack of significant disparities in bone health between individuals utilizing emicizumab and those who are not. Furthermore, our findings suggest that emicizumab usage does not lead to a decline in bone health over the observed period.

Figure



Table

	Hemophilia A emicizumab user (n=8)	Hemophilia A, emicizumab naïve (n=16)	Hemophilia B (n=10)	P valve
Age	37.5 (16-53)	46 (20-70)	42 (24-66)	0.804
ABR	1.5 (0-23)	2.5 (0-97)	4 (0-25)	0.638
BMD Lumbar spine	0.10 (-2.5-3.4)	-0.25 (-2.9- 1.2)	-0.3 (-2.0-3)	0.385
BMD femur	-0.7 (-2.2-1.5)	-1.0 (-3.6-1.9)	-1.0 (-2.4-0.5)	0.978
BMD hip	-1.15 (-2.0-1.5)	-1.0 (-3.2-1.8)	-1.0 (-2.0-0.7)	0.978
P1NP (ng/mL)	47.03 (26.78-105.5)	45.19 (24.05-124.00)	67.295 (38.88-96.30)	0.050
CTX (ng/mL)	0.536 (0.326-.875)	0.398 (0.159-0.767)	0.458 (0.329-0.919)	0.820
HJHS	14.50 (2-36)	17 (1-50)	10 (2-27)	0.868
HEAD-US	22 (5-41)	24 (1-42)	14.5 (6-31)	0.309

Data (median, range); ABR: annual bleeding rate; BMD: bone mineral density; P1NP: procollagen type 1 N-terminal propeptide; CTX: C-terminal telopeptide; HJHS: hemophilia joint health score; HEAD-US: hemophilia early arthropathy detection–ultrasound

Note

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Note

Note

選擇CABLIVI 從第一天開始

合併血漿置換術
及免疫抑制劑

ISTH
治療指引
建議使用
CABLIVI[*1]

CABLIVI 適用於合併血漿置換術及免疫抑制劑，治療患有後天性血栓性血小板低下紫斑症 (acquired thrombotic thrombocytopenic purpura; aTTP)[‡] 之成人及12 歲以上且體重40公斤以上的青少年病人[3]

Cablivi
caplacizumab

*假設 aTTP 的可能性很高 (基於臨床評估或正式的臨床評估工具) 並能及時進行ADAMTS13測試[1,2]
†合併血漿置換術及免疫抑制劑
‡aTTP 亦或稱為 iTTP, 兩者可能被互換使用[5]

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13; aTTP=acquired thrombotic thrombocytopenic purpura; ISTH=International Society on Thrombosis and Haemostasis; iTTP=immune-mediated thrombotic thrombocytopenic purpura; MAHA=microangiopathic hemolytic anemia; PEX=plasma exchange.

References: 1. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18(10):2486-2495. doi:10.1111/jth.15006 **2.** Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18(10):2496-2502. doi:10.1111/jth.15010 **3.** CABLIVI TFDA Approved Package Insert, Nov. 2023 **4.** Joly BS, et al. Thrombotic thrombocytopenic purpura. Clinical Platelet Disorders. Blood (2017) 129 (21): 2836–2846. doi:10.1182/blood-2016-10-709857 **5.** Kucukyurt S, Eskazan AE. Assessment and Monitoring of Patients with Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP): Strategies to Improve Outcomes. J Blood Med. 2020; 11: 319–326. doi: 10.2147/JBM.S205630

簡易仿單
【藥品許可證字號】衛部菌疫輸字第001243號，本藥限由醫師使用
【中英文品名】可利康®凍晶注射劑10毫克，Cablivi 10 mg powder and solvent for solution for injection。【主要成分】Caplacizumab【處方資訊摘要】[詳細內容請參照衛生福利部核准之完整產品說明書內容] 【適應症】適用於合併血漿置換術及免疫抑制劑，治療患有後天性血栓性血小板低下紫斑症（acquired thrombotic thrombocytopenic purpura; aTTP）之成人及12歲以上且體重40公斤以上的青少年病人。【劑量與給藥方式】Cablivi治療應由具有處置血栓性微血管病變病人之經驗的醫師開立處方及監督。劑量 第一劑：至少於血漿置換治療15分鐘前，以靜脈注射方式投予10 毫克的caplacizumab。後續劑量：於每天血漿置換治療期間，完成各次血漿置換之後，以皮下注射方式投予10 毫克的caplacizumab；接著於停止每天血漿置換治療之後，每天以皮下注射方式投予10 毫克的caplacizumab，持續30天。這個階段結束時，如果證據顯示有未緩解的免疫疾病，建議將免疫抑制療法最佳化，並繼續每天皮下注射10 毫克caplacizumab，直到所有免疫疾病徵兆緩解為止(例如ADAMTS13活性濃度持續正常化)。在臨床試驗中，Caplacizumab每天投予最多持續71天。延遲劑量 如果延遲Cablivi的投藥時間，可在12小時內施打。如果距原本應投藥時間超過12小時，則不應施打延遲的劑量，應依照原本的給藥時間表施打下一次劑量。【劑型與劑量強度】每小瓶含有10 毫克的caplacizumab白色凍晶粉末。【禁忌】對有效成分或所列的任何賦形劑過敏。【警語與注意事項】出血：Cablivi會增加出血風險。在使用caplacizumab的病人，主要為併用抗小板藥物或抗凝血藥物族群，有嚴重出血的案例被報導，包括危及生命及致命性的出血。在有誘發較高出血風險的病人身上，應小心使用caplacizumab。若臨床發現上有明顯出血，應暫停使用Cablivi。若需要，應考慮使用濃縮von Willebrand Factor來回復止血功能。只有在有處理血栓性微血管病變(thrombotic microangiopathies)的醫師建議下，才可以回復使用Cablivi。回復使用 Cablivi後應密切監測出血症狀，併用口服抗凝血劑、抗血小板藥物、血栓溶解劑，或肝素的病人 併用Cablivi及影響止血，凝血功能的藥物會增加出血的風險。初始或持續併用口服抗凝血劑 (如 維生素K拮抗劑，直接口服抗凝血劑[DOAC]，比如：凝血酶抑制劑或凝血因子Xa抑制劑)、血栓溶解劑如血酸溶素 [urokinase]、組織胞漿素酶活化劑 [tissue plasminogen activator [t-PA] (如：alteplase)]、抗血小板藥物或肝素，需要謹慎評估並密切監測。對於凝血功能異常的病人：由於可能增加出血風險，因此Cablivi用於具有既有凝血功能異常的病人(例如血友病，其他凝血因子不足)時，需進行密切臨床監測。對於將進行手術的病人：如果病人將進行非急迫性手術、侵入性牙科治療，或其他侵入性治療，應請病人告知醫師或牙醫自己正接受 caplacizumab 治療，且應在預定的侵入性療至少7天前停止使用。病人也應將預定的手術程序告知醫師Cablivi治療的醫師。在手術出血風險解除後，病人重新使用 caplacizumab 時，須密切監測病人出血的症狀。如果需要進行緊急手術，應考慮使用濃縮von Willebrand Factor來回復止血功能。重度肝功能不全病人：Caplacizumab並未針對重度急性或慢性肝功能不全的病人進行正式試驗，也沒有caplacizumab用於這些族群的相關資料。對此族群使用Cablivi時，需評估效益/風險並進行密切臨床監測。【交互作用】並未進行用以評估caplacizumab與口服抗凝血劑(例如維生素K拮抗劑，直接口服抗凝血劑(DOAC)，比如凝血酶抑制劑或凝血因子Xa抑制劑)、抗血小板藥物、血栓溶解劑如血栓溶酶 (urokinase)或t-PA(如，alteplase)，或高劑量肝素併用之藥物交互作用研究[見第5.1節併用口服抗凝血劑、抗血小板藥物、血栓溶解劑、或肝素的病人]。【懷孕】如果用藥過量，依據caplacizumab的藥理學作用，有可能增加出血風險。【懷孕與哺乳】懷孕：尚無孕婦接受caplacizumab治療的資料。充足試驗顯示caplacizumab對母鼠或胎兒均無影響[見數據]。作為預防措施，建議避免於懷孕期間使用Cablivi。哺乳：尚無哺乳中的女性接受caplacizumab治療的資料。目前尚不清楚caplacizumab是否會分泌至人類乳汁中。無法排除對孩子造成風險的可能性。必須決定是否停止哺乳或放棄/停止療法；決定時必須將孩子的哺乳效益及女性的治療效益納入考量。【不良反應】在 TITAN 及 HERCULES臨床試驗中最常見的不良反應為鼻出血、頭痛和牙齦出血。最常見的嚴重不良反應為鼻出血。非常常見，每10人中可能影響多於1人：牙齦流血、發燒、痣累、頭痛、流鼻血、尊麻疹。常見，每10人中可能影響1人：眼睛流血、吐血、血便、黑色，柏油樣便、胃出血、疼痛流血、直腸出血、注射部位反應：皮疹、癢癢，以及流血、腸部出血、症狀可能是快速發作的嚴重頭痛、噁吐、意識程度下降、發燒，有時為顱腦血管部癢硬或腦部疼痛、肌肉疼痛、中風、血尿、經血過多、陰道出血、視血、呼吸短促、瘀血 【藥理學特性】藥物治療類別：其他抗血栓藥劑，ATC碼：B01AX07。Caplacizumab是人源化二價奈米抗體，具有兩個相同的人源化建構組件 (PMP12A2hum1)，利用基因重組以三個丙胺酸構成的連接子相連，作用標的為von Willebrand factor的A1結構域（domain），可抑制von Willebrand factor與血小板之間的交互作用。因此，caplacizumab可避免超大（ultralarge）von Willebrand factor介導之血小板黏附，遠正是aTTP的特徵。其也會影響von Willebrand factor的動態（disposition），導致治療期間von Willebrand factor抗原的總量短暫降低，以及伴隨第八凝血因子活性(factor VIII:C)的降低。
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【適應症】 Hemlibra 適用於帶有或未帶有第八凝血因子抗體的 A 型血友病 (先天性第八凝血因子缺乏) 病人之出血事件常規性預防。**劑量及用法** 應在有血友病及/或出血性疾病治療經驗之醫師的監督下開始進行治療。劑量：應於開始使用 Hemlibra 治療的前一天停止使用繞道治療劑 (如 aPCC 與 rFVIIa) 治療 (包括常規性預防治療)。建議劑量為於最初 4 週每週一次投予 3 mg/kg (負荷劑量)，之後改為每週一次 1.5 mg/kg、每 2 週一次 3 mg/kg 或每 4 週一次 6 mg/kg 的維持劑量，且所有劑量皆應皮下注射給藥。用法：Hemlibra 僅供皮下注射使用，且應採用適當的無菌技術投藥。僅限注射於建議的注射部位：腹部、上臂外側及大腿。將 Hemlibra 皮下注射劑注射於上臂外側時，應由照顧者或健康照護專業人員來進行。輪換注射部位可能有助於預防或減輕注射部位反應。Hemlibra 皮下注射劑不可注入皮膚有發紅、瘀傷、觸痛或硬化等現象的區域，或是有痣或疤痕的區域。**【禁忌】**對活性成分或 Hemlibra 賦形劑過敏。**【警語及注意事項】**可追溯性 (traceability)：為了提高生物醫藥產品的可追溯性，應清楚記錄所投予產品的名稱和批號。與 Hemlibra 及活化凝血酶原複合濃縮物 (aPCC) 相關的血栓性微血管病變 (TMA)：對接受 Hemlibra 預防性治療的病人投予 aPCC 時，應監視是否發生 TMA。如果出現與 TMA 相符合的臨床症狀及/或實驗室檢驗發現，醫師應立即停用aPCC，中斷 Hemlibra 的治療，並視臨床需要進行處置。與 Hemlibra 及活化凝血酶原複合濃縮物相關的血栓栓塞：對接受 Hemlibra 預防性治療的病人投予 aPCC 時，應監視是否發生血栓栓塞。如果出現與血栓事件相符合的臨床症狀、造影檢查結果及/或實驗室檢驗發現，醫師應立即停用 aPCC，中斷 Hemlibra 的治療，並視臨床需要進行處置。接受 Hemlibra 預防性治療之病人的繞道治療劑使用指引：應於開始使用 Hemlibra 治療的前一天停止使用繞道治療劑。如果在進行 Hemlibra 預防性治療期間須使用繞道治療劑，醫師應向所有病人及/或照顧者說明準備使用之繞道治療劑的確切劑量與用藥時程。Hemlibra 會提高病人的凝血能力。因此，所需要的繞道治療劑劑量可能要低於未合併進行 Hemlibra 預防性治療之情況下所使用的劑量。使用繞道治療劑治療的劑量與療程須視出血的位置與程度及病人的臨床狀況而定。除非沒有其他的治療選擇/替代藥物，否則應避免使用 aPCC。Emicizumab 對凝血試驗的影響：Emicizumab 會取代活化態第八凝血因子 (FVIIIa) 的 tenase 輔因子活性。以內源性凝血 (包括活化凝血時間 [ACT]、活化部份凝血活酶時間 [如 aPTT]) 為基礎的凝血實驗室試驗可檢測總凝血時間，包括透過凝血酶 (thrombin) 將 FVIII 活化成 FVIIIa 所需要的時間。使用 emicizumab 時，這類以內源途徑為基礎的試驗就不須經過凝血酶的活化，因此會測得過度縮短的凝血時間。**【不良反應】**在安全性概況摘要：最嚴重的藥物不良反應 (ADRs) 為血栓性微血管病變 (TMA) 與血栓事件，包括海綿竇血栓 (CST) 與表淺性靜脈血栓合 併皮膚壞死。使用至少 1 劑 Hemlibra之病人發生最常見且有 ≥10% 通報的 ADRs 為：注射部位反應、頭痛與關節痛。
兒科族群目前尚無任何用於< 1 歲之幼童的資料。
參考仿單：HEMLIBRA SmPC 202203 使用前詳閱說明書，警語及注意事項
北市衛藥廣字第112050225號

血甯博®皮下注射劑150毫克/毫升
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HEMLIBRA® SC Injection 30 mg/mL
包裝：30 mg/1 mL
衛部菌疫輸字第001086號

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