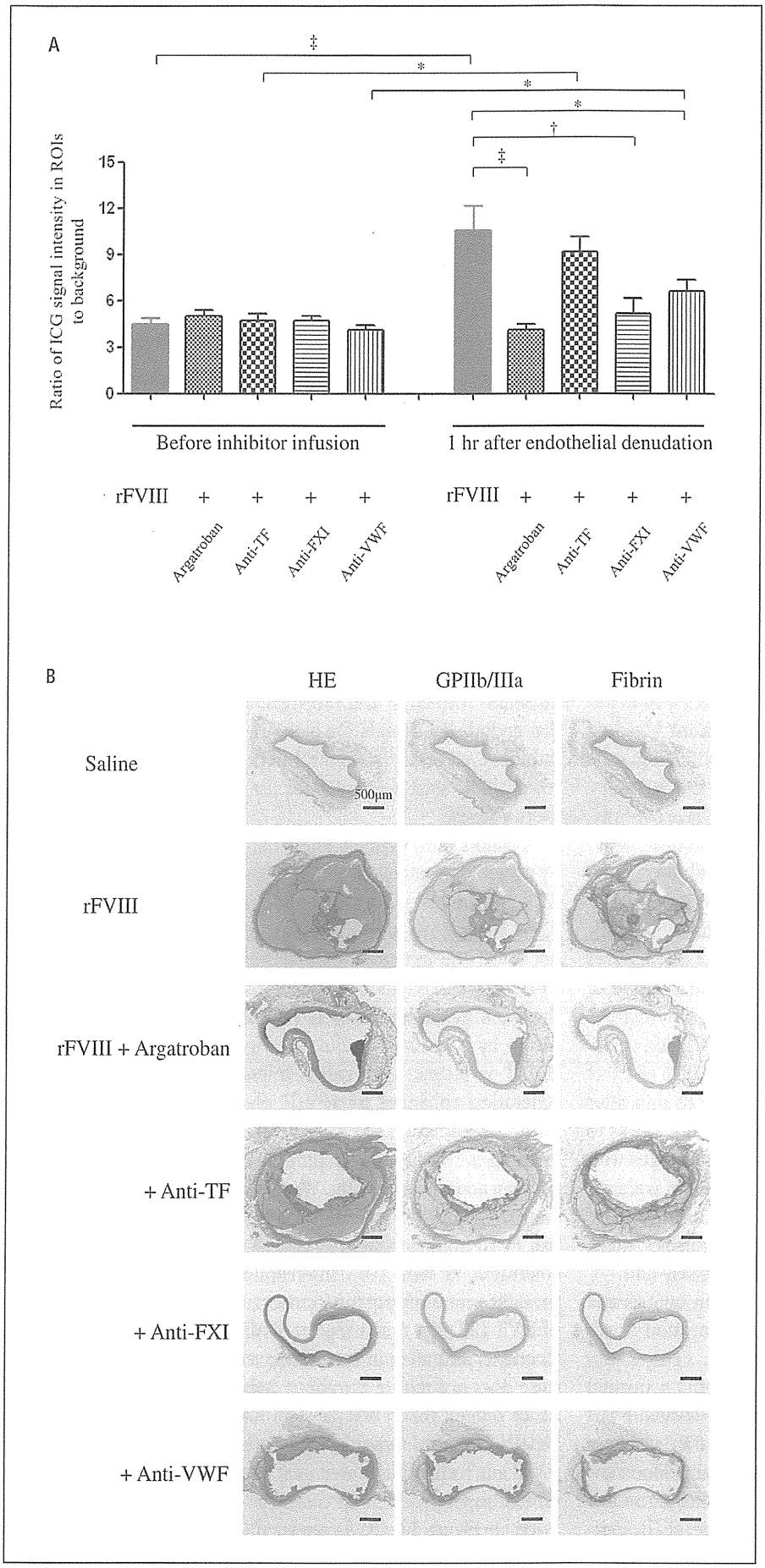

Figure 8: Thrombin, FXI and VWF, but not TF are required for thrombus growth after mural thrombus formation in rabbit jugular vein. A) Venous growth was monitored over time as fluorescence intensity of ICG after endothelial denudation with rFVIII infusion. Argatroban, anti-TF, anti-FXI and anti-VWF antibodies were infused when average fluorescence intensity of ICG exceeded three-fold background. Differences in average fluorescence intensity of ICG before inhibitor administration and 1 h after endothelial denudation are evident (*$p < 0.05$, †$p < 0.01$, ‡$p < 0.0001$, $n = 4$ each). B) Representative light and immunohistochemical microphotographs of venous thrombi. Administration of argatroban, anti-FXI, and anti-VWF antibodies after mural thrombus formation reduced further thrombus formation enhanced by rFVIII infusion.

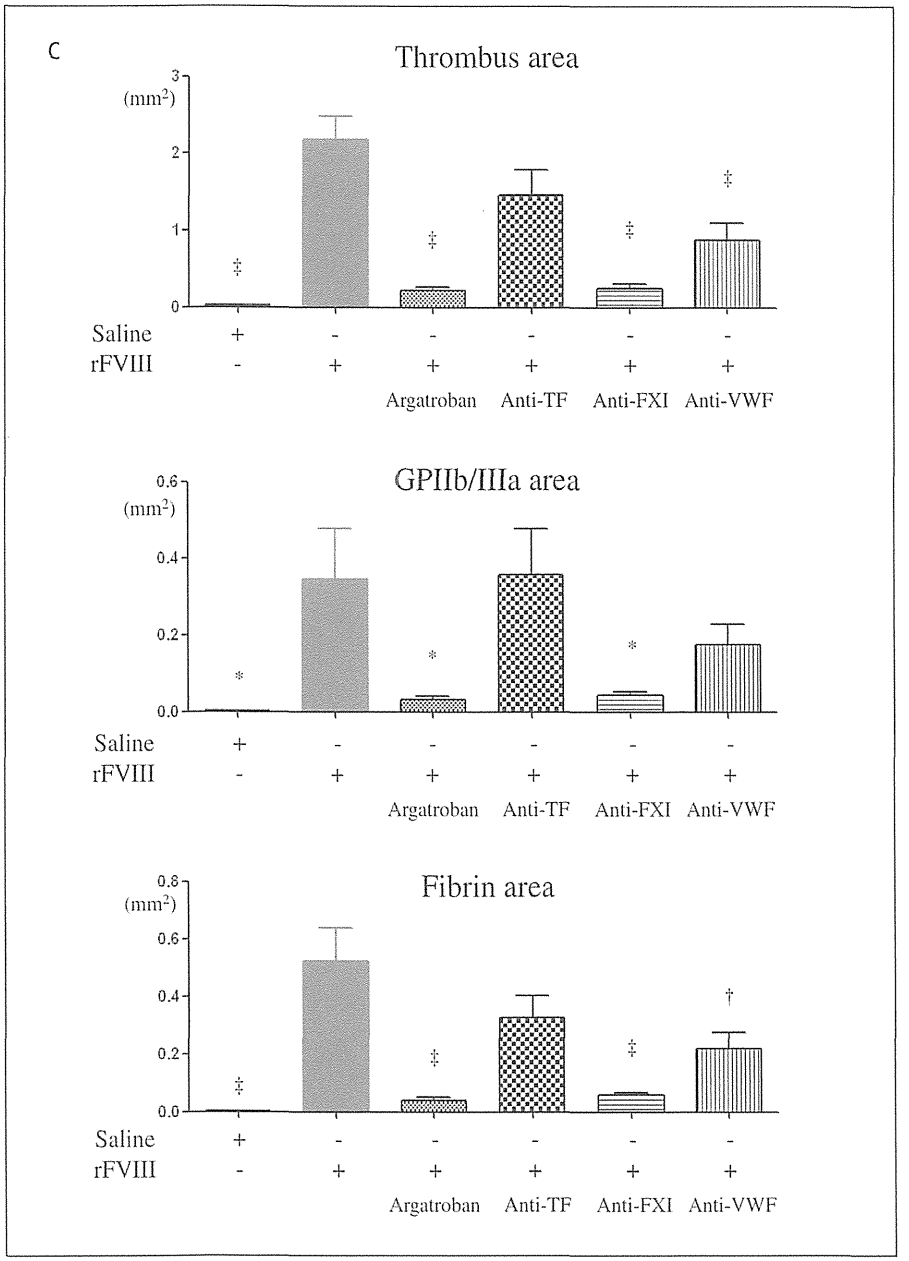

Figure 8 continued: C) Areas of thrombi, and GPIIb/IIIa and fibrin immunopositive areas in thrombi of jugular veins (*p < 0.05, †p < 0.01, ‡p < 0.0001 vs rFVIII group, n = 10 sections each).

face at a high, but not at a low shear rate, indicating that VWF might recruit FVIII on the surface of platelets but not of collagen under conditions of venous flow. This antibody also significantly suppressed venous thrombus propagation, but to a lesser extent than argatroban and anti-FXI antibody (▶Figure 8B and C). These results suggest that VWF-platelet interaction contributes principally to the initiation and somewhat to propagation of venous thrombus under high FVIII levels.

FXI is generally considered to be less important in normal haemostasis, because a bleeding tendency is mild or absent in patients with an inherited or acquired FXI deficiency (33, 34). However, recent studies indicate that FXI is activated during blood coagulation and that even small amounts of FXI induce thrombus growth by generating thrombin and by protecting thrombi from fibrinolysis via thrombin activatable fibrinolysis inhibitor (35, 36). Therefore, FXI apparently plays a significant role in thrombus growth and stability. Animal studies using $FeCl_3$- or vessel clamp-induced venous thrombosis models have shown that FXI plays a crucial role in thrombus propagation and stability (37-39). We and others (20, 40) have also demonstrated that FXI contributes to arterial thrombus propagation rather than to initiation. The present study found that anti-FXIa antibody reduced venous thrombus formation and propagation. FXI is mainly activated by thrombin and FXIa but not by factor XII on negatively charged surfaces (41). As thrombin generation is significantly promoted under high FVIII levels, FXIa could largely contribute to the initiation of thrombus formation as well as thrombus propagation in venous thrombosis.

Although studies have shown that TF contributes to venous thrombus formation and propagation (42, 43), the source of TF in

What is known about this topic?

- Elevated plasma FVIII levels are associated with an increased risk of deep venous thrombosis.
- However, whether elevated FVIII levels promote venous thrombus formation and/or propagation, and its association with other coagulation factors *in vivo* remain unclear.

What does this paper add?

- Elevated plasma levels of FVIII enhance venous thrombus formation and propagation.
- Excess thrombin generation by FXI and VWF-mediated FVIII recruitment might contribute to FVIII-driven venous thrombus growth.

venous thrombosis remains obscure. Mice with a severe TF deficiency have impaired thrombus formation after inferior vena cava ligation (44). Transplanting wild-type mice with low-TF bone marrow does not suppress venous thrombus formation and transplanting wild-type marrow into such mice does not accelerate thrombosis (44). This indicates that vascular wall TF rather than circulating TF is critical for venous thrombus formation. On the other hand, Von Bruhl et al. reported that TF derived from myeloid leukocytes contributes to venous thrombosis initiated by restricting blood flow in the inferior vena cava (45). In addition, TF derived from haematopoietic cells or neutrophils was responsible for thrombus formation and propagation in a laser-induced arteriolar injury model (46, 47). We found here that anti-TF antibody reduced the formation, but not the propagation of thrombus even in the presence of high FVIII levels. Plasma TF protein was undetectable in the rabbits and TF inhibition in blood did not affect whole blood coagulation (data not shown). Our results suggest that venous thrombus formation in this model mainly depends on venous wall TF rather than blood-derived TF. These controversial results could be due to differences among triggers of venous thrombus formation (endothelial denudation, vessel ligation, flow restriction or laser-injury), flow condition (absence, presence or restriction), and vascular bed (jugular vein, inferior vena cava, or arteriole).

Venous thrombi have been created in various animal models. Ferric chloride (48) and electrolytic model (49) are reproducible, but such chemical and physical reactions are far removed from the actual pathophysiology of DVT. Vein ligation with or without endothelial denudation (19, 50) allows the assessment of interaction between the venous wall and progression from acute to chronic thrombus, but has a disadvantage for evaluating the efficacy of therapeutic agents. The vein stenosis model (30) can form laminar thrombus in the presence of blood flow and mimics the clinical situation, but it has the disadvantage of variations in thrombus size and stability. Endothelial denudation without flow restriction induces small venous, but not occlusive thrombi. We applied this model to evaluate thrombus propagation under conditions of elevated FVIII levels.

In conclusion, our results suggest that elevated plasma levels of FVIII enhance venous thrombus formation, and that excess thrombin generation by FXI and VWF-mediated FVIII recruitment might contribute to FVIII-driven venous thrombus growth.

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Conflicts of interest

A. Harada, T. Kitazawa, K. Hattori are employed by Chugai Pharmaceutical Co., Ltd. C. Sugita, A. Yamashita, Y. Matsuura, T. Iwakiri, N. Okuyama, S. Matsuda, T. Matsumoto, O. Inoue, M. Shima, and Y. Asada have no conflicts of interest.

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短 報

急性リンパ性白血病のL-asparaginase療法関連凝固異常に対する国内外の支持療法の現状

小川千登世[1]，真部 淳[2]，小原 明[3]，石黒 精[4]

Key words : L-asparaginase, Coagulation disorder, FFP, Antithrombin

緒 言

L-asparaginase（L-asp）は生体内のアスパラギンをアスパラギン酸とアンモニアに分解し，アスパラギンを枯渇させることによってアスパラギン合成酵素を持たない腫瘍細胞の蛋白合成を阻害する薬剤であり，急性リンパ性白血病（ALL）治療のkey drugである。L-aspの重要な有害事象のひとつに凝固異常があり，antithrombin（AT）やfibrinogen（FG）の減少はしばしば観察される。これら凝固異常による血栓症や出血を予防するために，本邦では新鮮凍結血漿（fresh frozen plasma: FFP）やAT濃縮製剤がしばしば投与されてきたが，欧米では予防的FFP補充はあまり行われておらず，L-asp治療中の小児の検討ではFFP投与は凝固異常の改善に有益でないとの報告もある[1]。また，血漿成分のほぼ全ての成分を含むFFPにはFGだけではなく，アスパラギンも含まれるため，アスパラギン枯渇により効果を発揮するL-asp治療中のFFP輸注はL-aspの効果を減弱させる可能性がある[2]との指摘もある。

目 的

本邦におけるL-asp治療中の凝固異常に対する支持療法の実施状況，海外との差異を調査し，検討する。

方 法

日本小児白血病リンパ腫研究グループ（Japanese Pediatric Leukemia/ Lymphoma Study Group: JPLSG）および日本成人白血病研究グループ（Japan Adult Leukemia Study Group: JALSG）のホームページに掲載されている参加施設を対象に，実務担当者宛に往復はがきを送付し，L-aspを含むALL治療中の凝固異常に対する以下のアンケートを行った。

Q1-1. 血栓症や出血予防目的にFFP投与を行っているか

Q1-2. 行っている場合FFP投与の目安となるFG値はいくつか

Q2-1. 血栓症予防目的にATの投与を行っているか

Q2-2. 行っている場合AT投与の目安となるAT値はいくつか

Q3. FFPとAT以外に血栓症予防目的で投与する薬剤はあるか

また，同様の質問を海外の11の小児ALL治療施設にもe-mailにて送付し，回答を得た。

結 果

国内アンケート回収率は，小児JPLSG施設が123/180施設（68%），成人のJALSG施設が100/201施設（50%）であった。血栓症や出血の予防目的にFFP投与を行うと回答した施設は小児で57/123施設（46%），成人では86/100施設（86%）であった。FFP投与基準を図1に示す。成人では70/86施設がFG 100 mg/dl未満と回答したが，小児施設では100 mg/dl未満と答えた施設と50 mg/dl未満と答えた施設が各21施設ずつであった。一方，AT予防投与は小児では114/123施設（93%）で行われていたが，成人では63/100施設（63%）と小児比べて少なかった。図2に示すようにATの投与基準は小児と成人でほぼ同様の傾向であり，AT 70%未満が最多であった。

海外11施設（回答率100%）では，FG値を指標にFFP補充を行う施設は1施設（FG：50>）のみ，ATを値のみを指標として予防的補充を行う施設は3施設

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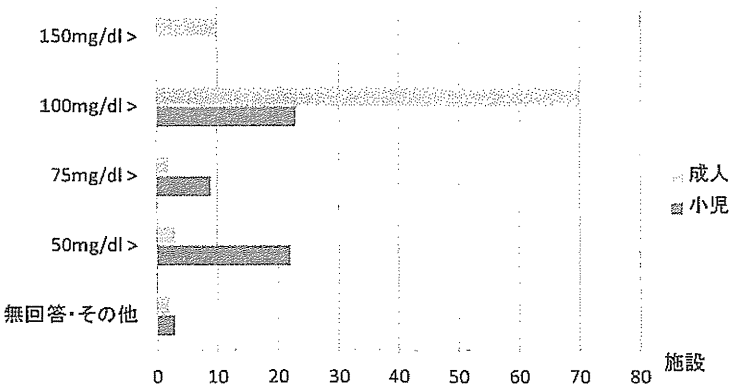

図1 FFP投与基準
FFP補充の基準は成人ではほとんどが100 mg/dl未満，小児では100 mg/dl未満と50 mg/dl未満がほぼ同数。

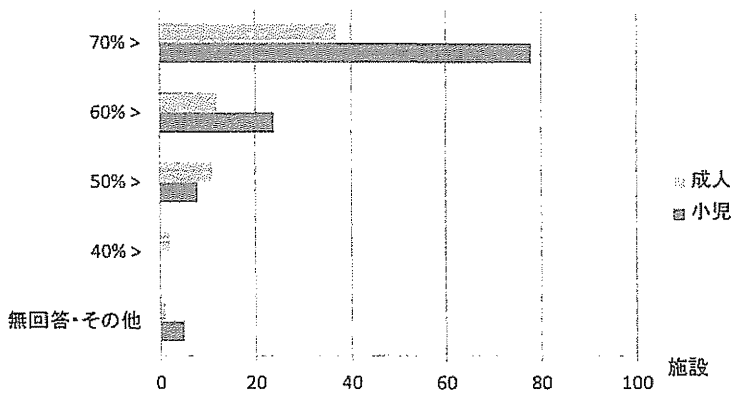

図2 AT投与基準
ATの補充基準は成人でも小児でも，70%未満が最多で，ほぼ同様の傾向。

(AT：70>，50>，40> 各1施設）であった。L-asp治療中であっても，凝固線溶系因子の定期的測定を行わないと回答した施設も6施設（55%）あった。

また，FFPやAT製剤以外に血栓症予防を目的に投与する薬剤があるかどうかの設問には，回答した国内212施設の76%がなしと回答，ヘパリンまたは低分子ヘパリン（LMWH）の併用を行っている施設は18%（39/212）であった。海外では3施設が血栓症発症後はLMWHを使用すると回答した。

考 察

本邦では凝固異常による血栓症や出血等の合併症を避けるために，FGやATの低下に対する補充療法が80年代から行われており，本調査でも成人施設の86%，小児施設の46%がFFPの，また，成人施設の64%，小児施設の93%がATの予防的投与を行っていた。一方，海外小児施設においてはFFPとATの予防投与実施率は9%と27%であった。

「血液製剤の使用指針」のFFPの適正使用の項には「低フィブリノゲン血症（100 mg/dl未満）の場合● DIC ● L-アスパラギナーゼ投与後」と記され，FFPは主に出血予防として使用される。しかし，L-asp治療中の凝固異常に起因する合併症の多くは中心静脈カテーテル関連の血栓症であり，最も危惧される中枢神経系の合併症でも出血は梗塞に続発する梗塞後出血であり，単独の出血の報告はほとんどない。米国でAbbottら[3]は，FFPまたはクリオプレシピテート予防投与を行うIWK Health Centerと，同じレジメンでALL治療を行うが，いずれの予防投与も行わないB. C. Children's Hospitalでの後方視的検討を行った結果，予防投与の有無で血栓症発症に有意差がないこと，また，低FG血症があってもFFP補充の有無によらず両群の全719例で1例も出血がないことを示した。

AT製剤予防投与の有効性は小児においてはいまだ証明されていないが，成人のCAPELAL studyでは寛解導入中のAT製剤の予防投与の血栓症発症率における有効性が，有意差（予防あり5% vs なし13%，$p=0.04$）をもって報告されている。

多くの海外小児施設は，FGやAT値の測定結果のみに基づく予防的補充療法は行っていない。特に英国では凝固異常の支持療法ガイドラインを定めて，予防的補充療法は実施せず，血栓症発症後の抗血栓治療もurokinaseでの溶解あるいはLMWH投与を基本とし，AT製剤投与は推奨していない。このガイドラインに従ったUKALL2003試験1,824例の小児ALLからは，3.2%が血栓症を起こしたが，一度血栓症を発症した症例もその後はLMWHを併用することで血栓症を再発することなく安全にL-asp投与継続ができることが報告された[4]。

ステロイドの長期投与が行われる寛解導入の後半には高脂血症もおこりやすく，特にL-asp投与終了直後には高度の高脂血症も観察される。また，凝固因子に比較して線溶系因子の回復が遅れる傾向があり，血小板数も回復してくる寛解導入終了時期のFFP投与は血栓症発症

のリスクになりうると考える。FFP 投与直後に血栓症を発症した報告[5] もあり，FG の半減期は FFP に含まれる他の抗凝固，線溶因子より長いため，投与直後は凝固線溶系がアンバランスとなる可能性もある。

結　語

本調査の結果，日本と海外の支持療法の方針には大きな違いがあり，日本では検査値に従った凝固因子補充が行われていることが明らかとなった。

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Current national and international status of supportive therapy for the coagulopathy associated with L-asparaginase containing regimen for acute lymphoblastic leukemia

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We investigated supportive therapy against coagulopathy associated with L-asparaginase treatment in patients with acute lymphoblastic leukemia who were enrolled in the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), Japan Adult Leukemia Study Group (JALSG), and foreign institutes. Fresh frozen plasma (FFP) was administered as a supplement in 46% patients in the JPLSG and 86% in the JALSG. The threshold level of FFP infusion was less than 100 mg/d*l* plasma fibrinogen in 70% of the JALSG and 20% of the JPLSG, while in another 20% of the JPLSG, FFP was administered when the fibrinogen level was less than 50 mg/d*l*. The preventive use of antithrombin products (AT) was prescribed in 93% of the JPLSG and 63% of the JALSG: The threshold level of AT supplementation was less than 70% of plasma antithrombin activity, which was similar in both groups. Most foreign institutes do not routinely use FFP or AT.