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Eptacog alfa activated: a recombinant product to treat rare congenital bleeding disorders

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ABSTRACT

Glanzmann's thrombasthenia (GT) and congenital factor VII deficiency (FVII CD) are rare autosomal recessive bleeding disorders: GT is the most frequent congenital platelet function disorder, and FVII CD is the most common factor-deficiency disease after haemophilia. The frequency of these disorders in the general population ranges from 1:500,000 to 1:2,000,000. Because GT and FVII CD are both rare, registries are the only approach possible to allow the collection and analysis of sufficient observational data. Recombinant activated factor VII (rFVIIa, eptacog alfa activated) is indicated for the treatment of acute bleeding episodes and for surgery coverage in patients with GT who are refractory to platelets and have antiplatelet or anti-human leukocyte antigen (HLA) antibodies, and for the prevention and treatment of bleeding in patients with FVII CD. This article summarises published data on the mechanism of action and use of rFVIIa in these disorders from two international, prospective, observational registries: the Glanzmann's Thrombasthenia Registry (GTR) for GT; and the Seven Treatment Evaluation Registry (STER) for FVII CD. Haemostatic effectiveness rates with rFVIIa were high across all patients with GT and those with FVII CD, and treatment with rFVIIa in the GTR and STER registries was well tolerated. The GTR and the STER are the largest collections of data in GT and FVII CD, respectively, and have expanded our knowledge of the management of these two rare bleeding disorders.

1. Introduction

Glanzmann's thrombasthenia (GT) and congenital factor VII deficiency (FVII CD) are rare autosomal recessive bleeding disorders, caused by platelet dysfunction in GT [1], and by structurally abnormal or deficient FVII in FVII CD [2]. Because both GT and FVII CD are rare, it is not possible to carry out controlled, prospective clinical trials [1]; instead, it is necessary to collect and analyse observational data. Patient registries are particularly useful for improving our understanding of the management of rare diseases: the largest patient registries for GT and FVII CD are the Glanzmann's Thrombasthenia Registry (GTR) [3–5] and the Seven Treatment Evaluation Registry (STER) [6,7], respectively.

Physiologically, FVII exerts its haemostatic effect after complexing with tissue factor (TF). In normal individuals, FVIIa-TF complex formation on TF-bearing cells at the site of vascular injury activates FX and FIX to trigger a series of events leading to an initial thrombin generation. The latter activates a variety of clotting factors (e.g., FV, FVIII, FXI) as well as platelets. Thrombin then induces local haemostasis by converting fibrinogen to fibrin, which polymerises and forms a thrombus in conjunction with platelets at the site of vascular injury. Thrombin can also be generated on the surface of activated platelets by the action of recombinant activated factor VII (rFVIIa, eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark), which is thought to promote haemostasis by activating FIX and FX when complexed with TF.

Recombinant FVIIa is prescribed for the treatment of bleeding episodes and the prevention of bleeding in those undergoing surgery or invasive procedures in patients with GT with refractoriness to platelets (and in some countries where platelets are not available) [8–10]. The objectives of this article are to present the methodologies used for the GTR and the STER, and to summarise published data on the effectiveness of rFVIIa in patients with GT and FVII CD. The article will also highlight the value and feasibility of such patient registries in the collection of data for rare bleeding disorders.

2. Glanzmann's thrombasthenia

2.1. Disease overview

Activated platelets are recruited to the site of vascular injury where they normally aggregate, an event mediated in part by the binding of soluble fibrinogen to the platelet surface α_{IIb}-β_3 integrin (originally termed glycoprotein IIb-IIIa [GPIIb-IIIa]), a fibrinogen receptor. Patients with GT have low levels of, or defective, surface α_{IIb}-β_3 integrin [1,11,12]; as a result, the small amount of thrombin generated leads to the failure of platelets to

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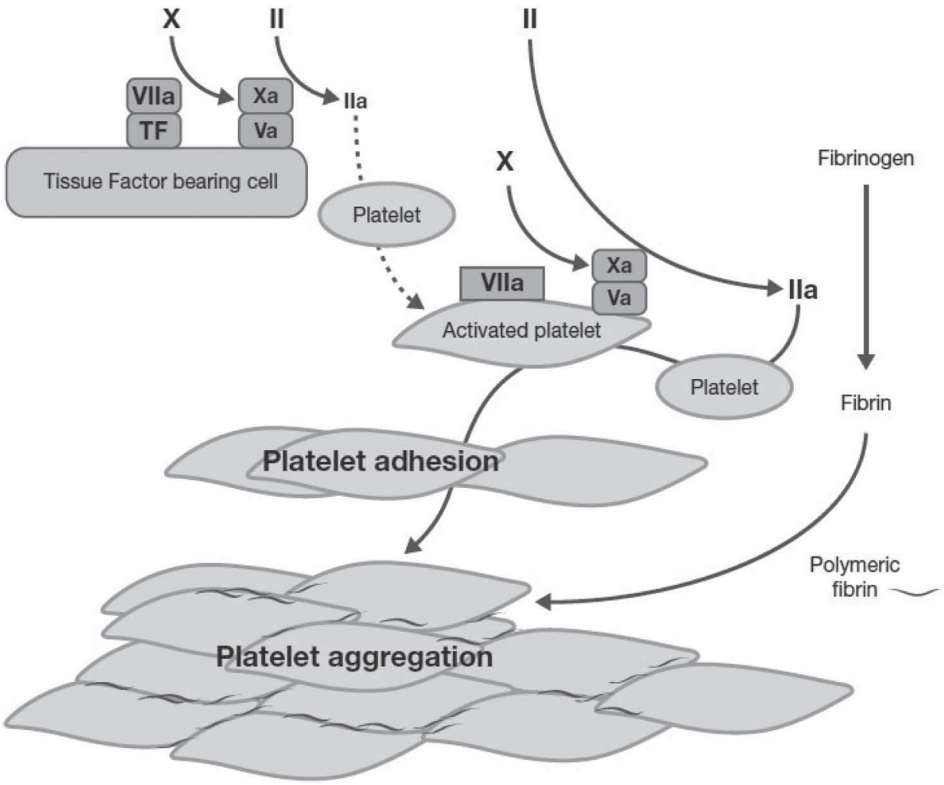

Fig. 1. Schematic tissue factor (TF)-independent, platelet-dependent model of primary haemostatic plug formation in Glanzmann's thrombasthenia (GT) platelets deficient in glycoprotein (GP) IIb-IIIa. Recombinant activated factor VII (rFVIIa) TF complex on TF-bearing cells at the site of vascular injury activates FX to FXa. FXa-FVa on the TF-bearing cells initiates generation of a small amount of thrombin (FIIa) that is insufficient to provide fibrin formation but sufficient to activate GT platelets, causing degranulation and release of FV. FVIIa binds weakly to the negatively charged phospholipid surface [49] of the activated platelets, with the binding enhanced by the GPIb/IX/V complex [50]. FVIIa at high concentration (attained by high-dose rFVIIa therapy) can directly activate FX to FXa to mediate generation of a high concentration of thrombin (thrombin burst). The augmented thrombin generation results in an increased number of activated platelets deposited (adhesion) to the wound site and in an increased available platelet procoagulant surface to facilitate more thrombin generation and more platelet activation. The augmented thrombin generated also converts fibrinogen to fibrin. GT platelets lack the fibrinogen receptor (α_{IIb}-β_3 integrin); therefore, these platelets cannot utilise fibrinogen for aggregation. However, binding of fibrin/polymeric fibrin to an unidentified platelet surface receptor can mediate aggregation of GT platelets at the wound site (albeit less potently than fibrinogen-mediated aggregation of normal platelets), resulting in the formation of a primary haemostatic plug (adapted from Poon [51] with permission)

bind fibrinogen, retract a fibrin clot or aggregate after stimulation by agonists such as adenosine diphosphate, thrombin, epinephrine and collagen at sites of vessel injury. Consequently, clot formation, and in turn retraction, fail. The incidence of GT is approximately 1:1,000,000, but is much higher in populations where consanguineous marriages are common [1,13].

GT is associated with well-defined sites of bleeding, including epistaxis, menorrhagia, gingival haemorrhage, easy bruising and ecchymosis [1]. Gastrointestinal (GI) bleeding and haematuria are less common [1], and haemarthroses and deep haematomas seldom occur [13,14]. In general, spontaneous, unprovoked bleeding is uncommon in patients with GT; rather, haemorrhages are usually associated with physiological or pathological predisposing conditions [1]. In addition, excessive bleeding after trauma or minor/major invasive or dental procedures is a common, major problem in GT [12–14].

Severity and frequency of bleeding in GT is heterogeneous, ranging from minimal bruising, to frequent, severe, potentially fatal haemorrhages [1,12,14]; this variability is seen even in siblings. The expression and functionality of the mutated α_{IIb}-β_3 integrin have been used to classify GT as type 1 (α_{IIb}-β_3 integrin expression <5%), type 2 (5–20%) or variant (>20–100%, but with a dysfunctional α_{IIb}-β_3 integrin) [14]. This classification does not fully predict bleeding phenotype, however, and the risk of severe bleeding remains unpredictable [1].

Standard treatment for GT is platelet transfusion – for persistent or severe bleeding, and for haemostatic cover of major invasive procedures [13–16]. However, platelet transfusion in patients with GT is associated with the potential development of isoantibodies against α_{IIb}-β_3 integrin and/or human leukocyte antigen (HLA), rendering further transfusions ineffective [14,16]. Platelet storage may also result in a series of side-effects such as fever, sepsis, thrombosis and acute lung injury [17]. In addition, platelet transfusion leaves patients at risk of blood-borne pathogen contamination related to the use of blood products [18].

In patients with GT, rFVIIa is recommended, administered as a bolus injection of 90 μg/kg [8–10]. While the mechanism of action of rFVIIa in GT is not fully understood [16], it is thought that rFVIIa improves local thrombin generation by direct activation of FX on the platelet surface (Fig. 1); rFVIIa treatment partially restores platelet aggregation, possibly via other membrane receptor pathways [16,19,20]. Although rFVIIa treatment does not result in a stable platelet plug, it does provide an increase of procoagulant surface at the site of injury, thereby facilitating additional enhancement of thrombin generation and subsequent fibrin formation [16].

2.2. Glanzmann's Thrombasthenia Registry

Prior to the European Medicines Agency (EMA) approval of rFVIIa for GT patients with inhibitors, a small clinical trial of rFVIIa was conducted in four patients [21], and a larger international survey of its efficacy and safety was subsequently conducted in 59 patients with GT (34 surgical/invasive procedures and 108 bleeding episodes) [22]. The results of the