Haemophilia B is clinically less severe than haemophilia A: further evidence

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Haemophilia A and B are rare bleeding disorders caused by mutations in the genes encoding coagulation factor VIII (FVIII) and factor IX (FIX)[1]. The prevalence of haemophilia A is 1 in 5,000 males in the general population, while that of haemophilia B is 1 in 40,000[1,2]. Patients with plasma factor levels <1 IU/dL are classified as having severe haemophilia, while those with levels between 1-5 IU/dL and >5 IU/dL as having moderate or mild haemophilia, respectively[2]. Patients with mild haemophilia bleed excessively only after surgery, tooth extractions or major injuries, whereas patients with moderate haemophilia bleed even after relatively minor trauma and those with severe haemophilia bleed spontaneously or after trivial trauma. Severe haemophilia is characterised by limb- or life-threatening symptoms such as haemarthrosis, soft-tissue haematoma, retroperitoneal and intracerebral haemorrhage and post-surgical bleeds. Complications from recurrent joint bleeding and soft-tissue haematomas include severe arthropathy, muscle contractures and pseudotumours, leading to chronic pain and disability that often warrant the intervention of the orthopaedic surgeon[3-5]. All these complications can be effectively prevented by the regular intravenous infusion of plasma-derived or recombinant products containing the deficient coagulation factor, and this prophylactic regimen is the mainstay of modern haemophilia care[6-8].

Traditionally, haemophilia A and haemophilia B have been considered clinically indistinguishable. However, beyond the perceptions of physicians working in haemophilia treatment centres, there is some evidence that severe FIX deficiency (<1 U/dL) may be clinically milder than the corresponding degree of FVIII deficiency[9,10], as summarised in the following points.

1) *Less severe gene mutations*. The most important factor contributing to the severity of haemophilia is the type of mutation. Thus, while null mutations (inversions, nonsense mutations and gross deletions) result in the total absence of FIX production, non-null mutations (missense mutations, single base pair deletions and insertions) may permit the synthesis of tiny amounts of residual protein[11,12]. Null mutations are prevalent in severe haemophilia A (~80%), whereas missense mutations are prevalent in severe haemophilia B (~60%)[13,14]. The fact that the latter are more frequent in severe haemophilia B supports the view that some FIX coagulation activity may be synthesised in these patients, thus attenuating the severity of the bleeding phenotype. Notably, the close correlation between non-null mutations and a milder clinical phenotype in severe haemophilia was recently demonstrated by Santagostino and colleagues in a case-control study[15].
2) *Less severe clinical symptoms*. In the framework of a process meant to develop a score in order to express the varied clinical severity of both types of haemophilia (Haemophilia Severity Score, HSS), Schulman and colleagues demonstrated that the HSS was higher in patients with severe haemophilia A than in those with severe haemophilia B[16]. Moreover, in a retrospective survey of joint arthroplasty conducted in 29 Italian haemophilia centres, Tagariello and colleagues[17]showed that patients with severe haemophilia A had a 3-fold higher risk of undergoing arthroplasty, which should be considered a proxy of the severity of arthropathy. Furthermore, in a Canadian study[18] it was found that patients with severe haemophilia B bled less frequently than patients with haemophilia A, and a more recent Italian study[19] demonstrated that patients with haemophilia B had fewer haemarthroses and lower World Federation of Hemophilia ultrasound scores. More indirect but important evidence suggesting clinical differences in severity between haemophilia A and B stems from the analysis of the recent trials of long-acting FVIII and FIX products. The rate of bleeding episodes during the 12 months prior to study entry (annualised bleeding rate, ABR) was markedly lower in haemophilia B patients than in haemophilia A patients. For instance, in the phase 3 study[20] of a recombinant FIX Fc fusion protein (Alprolix, Biogen/Sobi, Cambridge, MA, USA) involving 123 previously treated patients with severe haemophilia B, the median ABR during on-demand treatment was 18.0 (range 5-50), in contrast with a median ABR of 27.0 (range 18-40) reported during on-demand

*Blood Transfus 2018; **16**: 121-2* DOI 10.2450/2016.0158-16

treatment in a study of a recombinant FVIII Fc fusion protein (Eloctate, Biogen/Sobi) in 165 previously treated patients with severe haemophilia A[21]. The ABR in patients treated on demand for the occurrence of bleeding episodes was rather low in two additional studies of long-acting FIX products, although it is currently impossible to compare these figures with those for the corresponding factor VIII products[22,23].

3) *Less factor consumption.* There is some evidence from various sources that patients with haemophilia B use less FIX for replacement therapy yearly than the corresponding patients with haemophilia A, even accounting for the different prevalence of the haemophilias. The previously mentioned Canadian study[18] demonstrated that patients with severe haemophilia B used approximately 20% less factor concentrate than those with haemophilia A. Concordantly, two recent publications on FVIII and FIX use around the world, which obtained data from the Marketing Research Bureau and from the World Federation of Haemophilia, reported a mean FIX use of 0.29 (±0.41) IU per person with haemophilia B and a mean FVIII use of 1.66 (±2.01) IU per person with haemophilia A[24,25]. Patients' registries and data from various sources also indicate that regular prophylaxis is actually implemented less frequently in haemophilia B, as shown indirectly by fewer studies published on this mode of treatment. Indeed, a study collecting data from the whole Canadian haemophilia population reported that a significantly higher proportion of patients with severe haemophilia A needed regular prophylaxis compared with those with severe haemophilia B (69 *vs* 32%)[26].

All in all, although the evidence presented here is not conclusive, there is a hint that severe haemophilia B may be clinically less severe than haemophilia A. These findings raise the question of when and at which dosages and intervals should prophylaxis be recommended to patients with severe FIX deficiency.

The Authors declare no conflicts of interest.

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