Outcome in moderate haemophilia: back to the past? Remarks on haemophilia A classification and treatment

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Prophylaxis in haemophilia is now considered the standard treatment in developed countries for children with severe haemophilia (factor deficiency <1 IU/dL) and Uijl *et al*.[1] in this issue of Blood Transfusion highlight the possibility that such an approach might also be applied to a subgroup of patients with moderate factor deficiency (factor level 1-5 IU/dL), but with an apparent more severe clinical phenotype. Two randomised controlled trials have been independently published in the last few years, demonstrating the advantages of prophylaxis compared to on demand treatment in patients with severe factor deficiency[2,3]. Furthermore the World Federation of Haemophilia has recommended prophylaxis as the best treatment for children with haemophilia and has invited national authorities and experts to endorse this treatment in care programmes for people with haemophilia[4]. Despite several advantages in terms of improved quality of life, reduction of bleeding episodes into the joints and consequently low risk for long-term disabling haemophilic arthropathy, there are some concerns about this strategy, related mainly to the high costs and the difficulty in managing very young children with poor venous access, often making invasive procedures necessary (indwelling central venous catheter, artero-venous fistula) with their inherent associated risks.

The study by Uijl *et al*.[1] shows that even patients with moderate disease may bleed frequently and clearly benefit from prophylaxis. However the analysis of these patients raises some concerns. Patients with a factor level of 2 IU/dL (group 2 in the study) had more frequent bleeds, received prophylaxis slightly more frequently, and had greater factor consumption (U/kg/year) than patients belonging to the group with a factor level of 1 IU/dL, who also used less factor VIII than the group with a factor level of 3 IU/dL, which is quite surprising and difficult to explain unless it is related to their older age. Given these results, the target factor level to achieve in patients with moderate deficiency would differ from that of patients with severe deficiency. However the major issue that this paper raises is whether a haemophilia classification based exclusively on plasma FVIII level, as stated by the Scientific and Standardization Committee in 2001[5], is still useful. Medicine is moving rapidly towards a personalised picture of signs, symptoms and laboratory results to reach a more precise diagnosis and tailored treatment. Haemophilia does not represent an exception and there are already examples of patients with severe factor deficiency, but with few bleeding episodes, often not affecting joints (so-called "mild-severe" patients)[6]. Thus, it should not be surprising to observe the reverse, i.e. patients with moderate deficiency and a severe clinical picture. The process of coagulation is complex involving mechanisms not completely understood. Other characteristics of the patient (pro-thrombotic polymorphisms, additional mild pro-haemorrhagic deficiencies, etc.) could significantly modify the patients' bleeding tendency. Furthermore, the recent report of a higher frequency of major surgery in patients with haemophilia B than in those with haemophilia A[7] has confirmed a possible difference between two inherited disorders, to date considered to share the same clinical and laboratory features. The more frequent prevalence of missense mutations in haemophilia B, which may produce consistent traces of plasma factor IX, could play a role in fostering better *in loco* coagulation inside joints than that in patients with severe haemophilia A who largely carry "null" mutations and do not produce any factor at all. To sum up, a more comprehensive definition of severity should probably take into account both phenotype and genotype. The combination of both might help a new classification of haemophilia A severity.

Further considerations should be taken into account: in the world nearly 80% of patients with haemophilia do not receive any treatment at all and also in Europe there are relevant differences between per capita factor VIII consumption between western countries (the Netherlands, France, Germany, Italy, etc.) and eastern ones (Poland, Hungary, Czech Republic, etc.). Hence, also in Europe increasing usage of prophylaxis in patients with moderate deficiencies raises ethical issues when a large proportion of patients with severe deficiency does not yet receive the standard, on demand amount of factor for replacement therapy.

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Finally, a puzzle: in the past, many people dealing with haemophilia in clinical practice considered patients with a factor deficiency <2 IU/dL to have a severe deficiency. Is the "new approach" actually a return to the past?

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