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Narrative Review

Progress in the contemporary management of hemophilia: The new issue of patient aging

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ABSTRACT

The management of inherited coagulation disorders such as hemophilia A and B has witnessed dramatic progresses since the last few decades of the last century. Accordingly, persons with hemophilia (PWH) now enjoy a life expectancy at birth not different from that of males in the general population, at least in high income countries. Nowadays, a substantial proportion of PWH are aging, like their peers in the general population. This outstanding progress is accompanied by problems that are in part similar to those of any old person (multiple concomitant diseases and the resulting intake of multiple drugs other than those specific for hemophilia treatment). In addition, older PWH suffer from the consequences of the comorbidities that developed when their treatment was at the same time poorly available and unsafe. Typical hemophilia comorbidities affect the musculoskeletal system following joint and muscle bleeds, but also the liver and kidney are often impaired due to previous bloodborne infections such as viral hepatitis and HIV. Thus, the comorbidities of hemophilia superimposed on the multimorbidity and polypharmacy associated with aging create peculiar problems in the current management of these patients, that demand the coordinated holistic intervention of internists, geriatricians and clinical pharmacologists in addition to the care traditionally provided by pediatricians and hematologists.

1. Introduction

Hemophilia 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 hemophilia A is 1 in 5000 male live births and that of hemophilia B is 1 in 40,000 [1,2]. Patients with plasma factor levels <1 IU/dL (<1% of normal) are classified as severe hemophilia, those with levels between 1 and 5 IU/dL (1–5% of normal) and those with >5 but <40 IU/dL (>5%–<40% of normal) are moderate and mild hemophilia [3]. Although the bleeding phenotype may be heterogeneous [4,5], this classification reflects rather closely the severity of clinical symptoms [6]. Traditionally hemophilia A and B have been considered clinically indistinguishable from each other [7–9]. Recent evidence, however, suggests that severe hemophilia B may have a milder clinical phenotype than severe hemophilia A [8,9], reflected by less factor consumption, less deleterious gene mutations and less need for orthopedic surgery [9]. The latter is often necessary in poorly managed patients with hemophilia (PWH) because recurrent bleeding into muscles and joints is the hallmark of severe disease. The long-term consequences of these bleeds are the development of arthropathy through synovial hypertrophy, cartilage destruction and bone damage [10], that leads to relevant physical and psychosocial handicaps [11]. This review provides a general overview of the current knowledge of the comorbidity and the multiple chronic diseases associated with aging that may occur in PWH who are becoming older as consequence of the improved management of hemophilia.

2. Progress in hemophilia treatment

In the 1950s and the 1960s, fresh frozen plasma (FFP) was the mainstay of treatment for both hemophilia A and B. Each unit of FFP contains small amounts of FVIII and FIX, so that large volumes of intravenously administered FFP were needed to stop bleeding episodes and patients were usually hospitalized for each treatment. The first major progress in disease management took place in the 1960s, following the discovery by Judith Pool that it was possible to concentrate FVIII by cryoprecipitation of plasma [14,15], and in the 1970s following the introduction in the market place of lyophilized coagulation factors for both the hemophilias. This permitted the development of specialized treatment centres and enabled home treatment programmes. The decade also saw the initiation in Sweden of prophylaxis regimens [16], as well as the discovery in Italy of the synthetic drug desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. The 1980s were the gloomy years of AIDS and hepatitis, but these scourges fostered research that led to the cloning of FVIII and FIX genes, i.e., the

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basis for the production of FVIII and FIX by recombinant DNA technology [17,18]. Progress in viral inactivation methods also made plasma factors much safer [19] and indeed since the late 1980s no clinically relevant pathogen has been transmitted by coagulation factor products [20].

In the 1990s recombinant FVIII (rFVIII) and recombinant FIX became available, at least in high-income countries [21]. In addition, bypassing products such as an activated prothrombin complex concentrate (APCC, FEIBA) and recombinant activated FVII (rFVIIa, NovoSeven®, Novo Nordisk A/S) permitted treatment of bleeding episodes in PWH who had developed such a serious complication as anti-FVIII inhibitory antibodies (inhibitors). The 1990s also saw the introduction of immune tolerance induction therapy. First implemented in Bonn (Germany) and based upon repeated and long-lasting infusions of FVIII [22,23], this demanding therapeutic approach is able to eradicate inhibitors in approximately two thirds of cases, albeit with huge costs for the community and a heavy burden for patients [24,25]. Finally, the recent development of FVIII and FIX recombinant products with extended half-life (EHL-FVIII and EHL-FIX) promises to further improve treatment by reducing the number of intravenous injections needed to maintain a trough prophylactic level of replacement factor. Some EHL factor products are already licensed or in an advance stage of clinical development [26]. EHL-FVIII products have an average increase in half-life of no more than 1.5 times compared to the standard FVIII products [27–30], whereas EHL-FIX products have a much more marked and clinically significant 3–5 fold increase compared to standard FIX products [31–33].

3. Achievements of replacement therapy

The forementioned availability of high-quality plasma-derived and recombinant factor products has greatly contributed to the improved quality of life and reduced morbidity in the hemophilia community. Further, life expectancy for PWH in high-income countries has matched that of the general population [35]. Comparing with the most frequent monogenic diseases (cystic fibrosis, thalassemia major, muscular dystrophy), PWH have a much better quality and expectancy of life [36].

The ultimate treatment goal in PWH is the prevention of bleeds, particularly of hemarthrosis with the resulting preservation of a normal joint status. To achieve this goal, patients with severe hemophilia A and B should be primarily managed with regularly spaced prophylactic infusions of coagulation factors or, when the latter treatment regimen is not available or feasible, with an aggressive and early demand treatment of the actual bleeding episodes with plasma-derived or recombinant FVIII or IX products. Several studies have demonstrated the superiority of prophylactic regimens with FVIII compared with on-demand treatment in severe hemophilia A [41–45]. The epitome of the efficacy of prophylaxis is a randomized study carried out in boys with normal baseline joint imaging, showing that prophylaxis with rFVIII administered every other day was effective in preventing structural joint damage (as detected by MRI). With this solid evidence of the efficacy of prophylaxis in patients with severe hemophilia A, in real-world clinical practice the dose and frequency of prophylactic FVIII infusions vary widely in PWH, ranging from alternate days [42] to three times a week [48] or two times a week [49].

Factor VIII half-life is 8–12 h and for FIX is 18–24 h [50], with much inter-individual but little intra-individual variations in pharmacokinetics [51]. In addition, there is some degree of patient heterogeneity in terms of clinical phenotype and responsiveness to treatment [40]. These characteristics led Canadian investigators to develop a tailored, dose-escalating prophylaxis regimen. All PWH were initially treated with rFVIII at a relatively large dose once weekly, until dosage escalation criteria were met when bleeding episodes were not satisfactorily prevented. If the criteria for dose escalation did apply, patients received rFVIII twice weekly and if any of the escalation criteria recurred again, rFVIII was given at alternate days. Results from the prospective clinical study carried out in boys with severe hemophilia A treated with this tailored regimen showed minimal joint change on physical examination and minimal functional disability over the 13 year study duration [52,53]. As expected, more subjects did escalate the frequency of infusions as they got older as a result of an increased bleeding frequency. Kaplan-Meier estimated probability of not escalating to the two times a week regimen was about 40% at 50 months and 20% at 150 months and the probability of not escalating further to the alternate day regimen was 40% at 150 months. Continued longitudinal evaluation of this cohort will yield further information regarding more long-term joint outcomes [53].

Furthermore, pharmacokinetic-driven approaches have been proposed to tailor prophylaxis regimens, using individual's pharmacokinetic (PK) responses to FVIII infusions to calculate dose and dosing frequency [54–56]. Dose regimens for prophylaxis are designed to keep the trough level of the replaced clotting factor above 1% of the normal level, because observational data indicate that the time per week spent by patients with FVIII/IX levels <1% is associated with an increased rate of bleeding [48]. A recent study has attempted to answer the question whether or not the rather cumbersome pharmacokinetic approach, that implies taking multiple blood samples in children is truly needed for the optimal tailoring of prophylaxis regimen, or whether a simpler fixed regimen is equally adequate. Results showed that the annualized bleeding rates for the fixed or tailored prophylaxis regimens were not different [57].

The rationale for prophylactic management of hemophilia originally developed in Sweden by the pioneer work of Nilsson and Blomback was based upon the transformation of the phenotype of severe hemophilia into that of moderate disease, because patients with moderate hemophilia typically bleed only in response to some trauma. Furthermore, patients with mild hemophilia bleed only in response to significant tissue injury induced by trauma or surgery. Thus, for the majority of mild and moderate hemophilia patients, replacement therapy is only employed on demand in order to control trauma related bleeding and to prevent bleeding before surgery or other invasive procedures.

4. The inhibitor complication

Development of alloantibodies neutralizing the coagulant activity of FVIII is currently the most serious and challenging complication in the management of hemophilia A. Inhibitors compromise the ability to control hemorrhage, resulting in increased morbidity and disability for patients and costs for the community. A study from the UK examined the epidemiology of inhibitors in relation to age and previous treatments among patients with severe hemophilia A [24]. The highest incidence of inhibitors pertains to children aged <5 years previously untreated (or minimally treated) with factor replacement therapy (64.3 cases per 1000 treatment-years). The incidence was much smaller (5.3 per 1000 treatment-years) in treated patients at age 10–49 years, rising to 10.5 per 1000 treatment-years in PWH >60 years of age [24]. Thus, the UK study shows that, at variance with previously untreated patients (PUPs), inhibitors are a rare event in previously treated patients (PTPs) with hemophilia A. Further, according to two recent meta-analyses, the pooled incidence rate of inhibitor development for the 25 studies providing follow-up data was 3 per 1000 person-years (95% confidence interval 1–4) [58,59]. Little is known about risk factors for inhibitors in PTPs, a field difficult to study due to the low incidence rate of this complication. There is no clear evidence of an increase of inhibitors when switching to and from the currently available factor concentrates, whether plasma-derived or recombinant [60].

With these preambles on the incidence of inhibitor in relation to age and treatment, it must be pointed out there are multiple risk factors for the development of this complication. In the high risk category of PUPs, residual plasma FVIII levels, gene mutations [61–63], early replacement therapy and the source of FVIII (i.e., human plasma or recombinant DNA technology) are the most clearly and consistently implicated risk factors [62,64–67]. The recently published Survey of Inhibitors in Plasma-

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