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Letter to The Editor

Continuity of Care in Haemophilia: Science, Not Emotion

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Hemophilia A and B are rare bleeding disorders caused by mutations in the *F8* and *F9* genes encoding the coagulation factor VIII (FVIII: C) and factor IX (FIX: C) [1]. The prevalence of hemophilia A is 1 in 5000 males in the general population that of hemophilia B is 1 in 40,000 [1]. The clinical severity of hemophilia correlates strictly with the degree of the defect of the corresponding coagulation factor, having individuals with FVIII: C or FIX: C levels below 1% the most severe hemorrhagic phenotype [1].

Life expectancy in hemophilia patients has drastically risen over the last decades, and today it is comparable, both in Italy and in the rest of the western world, to the general male adult population [2]. This excellent achievement (in the 1960s life expectancy was around 30 years) has been made possible by:

1. The large-scale availability of clotting factor concentrates, in particular those produced by recombinant DNA technology, which are safe from the point of view of infection as they do not contain human- or animal-derived proteins in the culture medium or in the final formulation (third generation products);
2. The adoption of prophylaxis as a treatment strategy;
3. The increasing adherence of patients to therapeutic regimens;
4. The availability of anti-viral treatment for HCV and, in particular, HIV infections.

At the start of the 1980s, the HIV epidemic had devastating consequences for hemophiliacs, many of whom were treated with plasma-derived concentrates infected with the virus. However, from the end of the 1980s the arrival of virus-inactivated plasma-derived products and especially recombinant products which then became available to an increasing degree, restored the patients' faith and allowed treatment strategies to be implemented aimed at normalizing life expectancy and quality of life. The availability of recombinant products (first, second and third generation products according to the progressive removal of human and animal proteins from the production process and final formulation) was instrumental in the diffusion of primary and secondary prophylaxis regimens in many countries, including Italy [3]. This radically shifted the paradigm of hemophilia care, treatment from treatment to prevention of bleeding and in particular of the harmful complications of bleeding into joints, thus ensuring psychological and physical well-being and normal social life in patients. The treatment options were therefore able to satisfy the two main requirements, efficacy and safety, those doctors and patients look for in treatment of a congenital disease which requires life-long treatment from infancy.

Thus, medical experts on hemophilia and the community of hemophiliacs have developed the concept of "continuity of care" intended as availability and maintenance of treatment with the FVIII and FIX concentrate that offers the best clinical benefit to each patient [4]. The principle of continuity of care has proved invaluable to the specialist medical community, because it offers a clear advantage linked to the traceability of each patient's treatment history [5]. In addition it has been used by hemophilia caregivers to scientifically demonstrate that which already seemed intuitive: when a patient feels protected by a product which they know to be safe and effective, adherence to treatment improves and consequently Quality of Life (QoL) increases [5]. This result is even more evident in the transition from adolescence to adulthood, when young hemophiliacs tend to reject change and to move away from prophylaxis [6]. It is well documented that, in the long-term, improved QoL leads to reduced costs in terms of expenses for complications [7]. In short, the patient receives adequate amounts of the clotting factor concentrate, knows and trusts the treatment having experienced efficacy and safety, rigorously adheres to prophylaxis, improves life expectancy and quality of life and creates savings for the National Health Service (NHS). The psychological aspect of therapy is tightly linked to the medical-scientific and economic aspects. The consideration that improved quality of life in hemophilia patients is associated with a reduction in costs has been demonstrated also by a recent study carried out by Kodra and colleagues (2014). The study showed

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that each point gained on the scale of the EQ-5D questionnaire to evaluate quality of life resulted in a reduction of costs of a total of €279, regardless of the age of the patient [8].

It is known that the choice of FVIII and FIX concentrate used in replacement therapy in hemophilia patients represents one of the problems that medical experts on hemophilia must face. Today there is a wide range of options to choose from, both among products derived from human plasma and those produced by DNA recombinant technology. All the reference guidelines in the field (Italian [9], European [10], and international [11]) recommend that the decision must be taken with the active and conscious involvement of the patient, which leads to the patient's informed consent. It has been demonstrated that patient preferences are most often oriented towards continuity of care [12], especially in cases in which the chosen clotting factor concentrate also offers advantages of longer half-life, better handling and transportability and ease of reconstitution [13,14]. It is interesting to observe how patients, in making a prophylactic treatment choice, clearly prefer a product which allows a lower number of infusions per week, rather than a product which can further reduce the frequency of bleeding [15]. Trust in known manufacturers in the field also plays a role in patient preference [15]. In short, the patient often develops a kind of "psychological dependence" on the product they use, which leads to reluctance to change the product [16]. A shared decision between patient and doctor gives the best guarantee of adherence.

At a particularly historic time for the treatment of hemophilia, with the introduction of new products with improved biochemical and/or pharmacokinetic properties, the recommendation of eminent experts that continuity of care can be preserved as far as possible and changes of products should be motivated by clear advantages for the patient, always as a shared decision [9,17] remains valid. Besides promoting adherence to treatment, the main reason behind this recommendation is the need for strict pharmacovigilance on plasma-derived and recombinant concentrates: we must not forget that the HIV and Hepatitis C epidemic of the 1980s is in part attributable to the scarce pharmacovigilance in place at the time. The need for strict pharmacovigilance became binding in the era of the epidemic of viral diseases being transmitted through plasma-derived products, and only a meticulous registration of exposure to various products and of batches used, allowed the at-risk batches to be identified and eliminated. Even though the risk of infection from concentrates can now be considered almost nil, our guard should never be lowered, as continual evidence of emerging pathogens proves [18]. The importance of pharmacovigilance in the area of hemophilia was affirmed in 2009 with the introduction of the European Haemophilia Safety Surveillance (EUHASS) by the European Association of Haemophilia and Allied Disorders (EAHAD), in which a description of all adverse events in patients with inherited bleeding disorders is provided, whether related or not to factor concentrate replacement treatment [19]. The surveillance is still active and most Italian hemophilia centers participate in it. The efficacy of pharmacovigilance, aimed at identifying intrinsic flaws in the product or numerous unexpected adverse reactions, is particularly important in the field of rare diseases, considering the low number of patients that receive the specific medicinal product. All manufacturers of clotting factor concentrate have an internal surveillance programme.

However, identification of long-term effects of medicinal products for rare diseases can require very long monitoring periods (see for example the surveillance for variant Creutzfeld-Jacob disease); the periods can be reduced by increasing the number of patients under surveillance. In this respect, continuity of care has the aim of maintaining the highest possible number of patients under surveillance and of shortening the monitoring periods [20]. In the United States, a Federal Biovigilance Control Group has been created which collects, analyses and publishes all the adverse events related to transfusions and organ transplants [21]. As an example of the results of pharmacovigilance in the area of blood derivatives, we note the identification, through patient data, of a strain of Hepatitis A which infected patients treated with a well-known factor IX concentrate; this last discovery led the manufacturer of the product to change the product packaging, reducing the risk of HAV infection [22]. The economic difficulties in which most European health services currently find themselves has put the spotlight back on the dilemma of product selection, also (or may be most of all) due to the cost, and makes the problem of switching more relevant than ever. The risk of inhibitor development (neutralizing antibodies) from switching from one concentrate to another has been a strong argument in favour of continuity of care for years. The available scientific evidence on the subject, although limited and not of a high level of quality, appears to be reassuring [16,23,24]. However, it is usually recommended not to change concentrate within the first 50 days of exposure to the medicinal product, which is the period in which inhibitor development risk is greatest, or during the preoperative phase of major surgery, as surgery represents a risk factor for inhibitor development. Switching products is not recommended in patients at high genetic risk of inhibitor development [23,24], and in those with a family history or history of inhibitor development [24]. The European Medicines Agency (EMA) requires that the possible reappearance of inhibitors (at a low level) after switching from one factor VIII product to another, in previously treated patients, even after >100 exposure days, and with positive history of inhibitors, is mentioned in the Summary of Product Characteristics (SPC) of factor VIII authorized for sale. For such patients, careful monitoring is recommended for the development of inhibitors in the event of any change in product [25]. This recommendation can reasonably be extended to all patients, especially if switching to new modified products, for which pharmacovigilance data is still extremely limited.

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