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LETTER TO THE EDITOR

Recently approved recombinant factor VIII (rFVIII) for the replacement treatment in patients with hemophilia A in Italy

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KEYWORDS

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HEMOPHILIA A

Inherited or acquired genetic mutation resulting in dysfunction or deficiency of factor VIII (FVIII) or acquired inhibitor that binds FVIII are causes of Hemophilia A, a rare bleeding disorder. Among patients with genetic Hemophilia A, up to one third of cases are the results of new mutations (not present in the mother's X chromosome) [1].

Dysfunction or deficiency of FVIII leads to an insufficient generation of thrombin by the FIXa and FVIIIa complex by means of the intrinsic pathway of the coagulation cascade. This mechanism, in combination with the effect of the tissue-factor pathway inhibitor, generates, depending on the level of FVIII activity, a relevant trend towards easy bruising or inadequate clotting of traumatic or even mild injury or, particularly in subjects with severe hemophilia, with spontaneous hemorrhage [1].

Hemophilia A is classified as mild, moderate, or severe depending on the amount of the clotting FVIII in blood. In severe hemophilia A, the FVIII levels are practically undetectable (<1%) causing chronic debilitating joint disease results from repeated hemarthrosis, synovial membrane inflammation, hypertrophy and, in some cases, destructive arthritis. In order to prevent functional disability, early replacement of coagulation factors through infusion is necessary. In most developed countries, the standard of care is the prophylactic therapy starting in young patients [1].

In Italy, from the epidemiological point of view, the National Register of Congenital Coagulation Disorders [2] reported in 2014 a prevalence of the disease of 6.4 per 100,000 inhabitants, it substantially confirms the findings of the "World Federation of Hemophilia"*;* of the 3,906 registered subjects with hemophilia A, 1,800 had the severe form.

Hemophilia A has a significant impact on patients' quality of life (school, work, private life) and [3,4] to date has no cure. Moreover, increased disability and quality of life impairment increase with increased age, higher reported bleed frequency and lower employment [4].

MANAGEMENT OF PATIENTS WITH HEMOPHILIA A

As stated in both the international guidelines (World Federation of Hemophilia) and the Italian guidelines (*Associazione Italiana Centri Emofilia*), the treatment for patients with hemophilia A consists in the intravenous administration of the deficient or absent factor (FVIII) [5,6]. At the moment two strategies are availabe: on demand treatment, consisting in the treatment of an ongoing hemorrhage by infusing FVIII (which allows a temporary correction of the FVIII deficiency) or prophylaxis (long-term, regular infusion of FVIII), which reduce the bleeding tendency, and, consequently, the negative consequences of the hemorrhages on the joints, maintaining the factor levels in circulation

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and avoiding spontaneous bleeds [5,6]. The administration of FVIII, which in the past was carried out in hospital setting, is currently carried out (after adequate training of the patient or caregivers) at home also thanks to the availability of biotechnologic drugs, leading to an improvement in the quality of life of the patients themselves and their families [7].

The approach currently recognised as the most suitable treatment for the prevention of joint complications is the prophylaxis, to be started early in children with severe hemophilia A; the benefits of such a treatment regime have also been demonstrated in adolescent and adult patients. Prophylaxis usually requires the administration of factor three times a week, or on alternate days, although the frequency of administration can vary, depending on the type of drug used and the response of the individual patient to that drug (pharmacokinetics) the bleeding phenotype and the patient's daily activities and life style.

Since 90's, the available treatments have improved in safety, with the use of plasma concentrations produced through increasingly sophisticated purification techniques, which undergo viral inactivation, to factors obtained with recombinant DNA technology, which have no protein of human or animal origin.

As recently in Italy three new drugs have been made available for the treatment and prophylaxis of bleeding in patients with hemophilia A, our aim is to compare drugs consumption for all the recombinant FVIII actually reimbursed by the Italian National Health Service (NHS).

Kovaltry®

Kovaltry® (octocog alfa, Bayer SpA) a full length recombinant human coagulation factor VIII (rDNA), is a purified protein that has 2332 amino acids; it is produced by recombinant DNA technology in baby hamster kidney cells (BHK) into which the human factor VIII gene has been introduced [8]. The new manufacturing advances allow the co-expression of the human chaperone protein heat shock protein 70 (HSP70); HSP70 is a chaperone protein that may increase FVIII expression by facilitating proper protein folding and improves cell survival by inhibiting apoptosis (i.e., programmed cell death). Kovaltry® is prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation and has undergone nanofiltration with a 20 nm filter. The addition of this method to the production process represents a further guarantee of safety, since it is able to remove even potential non-capsulated viruses, previously unknown pathogens and protein aggregates, thus reducing the risk of pathogen transmission.

The efficacy and safety of Kovaltry® were assessed in the LEOPOLD broad clinical development programme [9-11] that consisted of three international trials conducted on over 200 children, adolescents and adults with hemophilia A.

The use of Kovaltry® in prophylaxis demonstrated a decrease in the annualised bleeding rate (ABR) of about 97%, compared to the on-demand treatment (2 vs. 60 bleeds/patient/year; $p < 0.0001$) allowing the progression of the hemophilic arthropathy to be reduced [9].

The LEOPOLD I and LEOPOLD II trials also demonstrated that Kovaltry® allows effective prevention of bleeds both with 3 infusions per week (3x) and with 2 infusions per week (2x). In LEOPOLD I trial, 29% of patients received the prophylaxis regime with administration twice a week, while in LEOPOLD II trial 47% was randomized to receive this reduced prophylaxis regime. Moreover, about 30% of the patients in prophylaxis with Kovaltry® reported no bleeds during the observation period. In the LEOPOLD Kids Part A trial, 45,1% patients had no bleeds during the six months treatment period [11].

Regarding the immunogenicity, in Kovaltry® clinical trials conducted on more than 200 patients (children and adults) with severe hemophilia A (FVIII < 1%) and previously treated with FVIII ≥ 50 ED, no inhibitors were detected.

Elocta®

Elocta® (efmoroctocog alfa, Swedish Orphan Biovitrum srl) a recombinant human coagulation factor VIII, Fc fusion protein (rFVIIIFc), has 1890 amino acids. It is produced by recombinant DNA technology in a human embryonic kidney cell line (HEK) without the addition of any exogenous human or animal-derived protein in the cell culture process, purification or final formulation [12].

The safety, efficacy, and pharmacokinetics of Elocta® was evaluated in 2 multinational, open-label, pivotal studies [13,14]; median annualized bleeding rates estimates from a negative binomial regression model were 2.91 (the ABR was estimated using the negative binomial model) for subjects in the individualized prophylaxis arm, 8.92 for subjects in the weekly prophylaxis arm and 37.25 for subjects in the on demand treatment arm. No bleeding episodes were experienced in 45.3% of subjects while on individualized prophylaxis and in 17.4% of subjects while on weekly prophylaxis.

Afstyla®

Afstyla® (lonoctocog alfa, CSL Behring SpA), a single chain recombinant human factor VIII produced in Chinese hamster ovary (CHO) cells, is a single polypeptide chain with a truncated B-domain that allows for a covalent bridge to link the factor VIII heavy and light chains [15]. Registrative study in adults and adolescent patients determined the efficacy and safety in the prevention of bleeding events in prophylaxis of Afstyla® [16,17]. The study enrolled 175 previously treated patients (age: 12 to 65 years) with severe hemophilia A who accumulated a total of 14,306 ED with rVIII-SingleChain. A total of 146 subjects were assigned to a prophylaxis regimen and had a median ABR of 1.14. In the study conducted in pediatric population on prophylaxis (81 patients, age < 12 years), median ABR was 3.69 in both studies no patient developed an inhibitor or experienced an anaphylactic reaction.

Other recombinant products

The other recombinant products for the treatment of hemophilia A currently available in Italy, which represent the standard of care, are Advate® (octocog alfa from CHO protein free, Shire Inc.), Helixate NexGen® e Kogenate Bayer® (octocog alfa from BHK, Bayer SpA) Recombinate® (octocog alfa from CHO, with human albumin as stabilizer, Shire Inc.), Refacto AF® (moroctocog alfa from CHO protein free, Pfizer S.r.l.), NovoEight® (turoctocog alfa from CHO protein free, Novo Nordisk S.p.A.) and Nuwiq® (simoctocog alfa from HEK protein free, Octapharma Italy S.p.A.). For each of these drugs, the summary of product characteristics recommends a dosage of 20-40 IU/kg every 2/3 days [12,15,18-24] except for NovoEight® (turoctocog), which is recommended at a dosage of 20-40 IU/kg every two days or 20-50IU/kg 3 times a week [25].

COMPARISON BETWEEN AVAILABLE TREATMENTS

Table I reports the annual average consumption per patient (dosage X number of administrations) of the available treatments based on European SPCs [12,15,18-25].
Data from clinical trials reported that for Kovaltry® the 30% of patients were treated with two administrations per week and for Elocta® this percentage account at 33%.
Even though the average number of administrations per years appears to be lower with Elocta®, if we consider the total consumption of drug per patient/year, in terms of IU, the results for an hypothetical patient with a weight of 70 kg are summarized in Figure 1.
As shown above , the use of Kovaltry® as indicated in the SPC (20-40 IU/kg 2-3 times a week) [24], allows to reduce the number of

Drug	Posology	Dosage (IU/kg)			Annual administrations (n.)			Annual consumption (IU/kg)		
		Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
Kovaltry® (octocog alfa from BHK protein free)	20-40 IU/kg 2-3 times a week	20	40	30	104	156	130	2,080	6,240	4,160
Advate® (octocog alfa from CHO protein free)	20- 40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Helixate NexGen® (octocog alfa from BHK)	20-40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Refacto AF® (moroctocog from CHO protein free)	20-40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Kogenate Bayer® (octocog alfa from BHK)	20-40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Recombinate® (octocog alfa from CHO)	20-40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Nuwiq® (simoctocog from HEK protein free)	20-40 IU/kg every 2-3 days	20	40	30	122	183	152	2,433	7,300	4,867
Elocta® (efmoroctocog from HEK protein free)	Dose adjustment from 25 to 65 IU/kg every 3-5 days	25	65	45	73	122	97	1,825	7,908	4,867
Afstyla® (lonoctocog alfa from CHO protein free)	20-50 IU/kg 2-3 times a week	20	50	35	104	156	130	2,080	7,800	4,940
NovoEight® (turoctocog from CHO protein free)	20-50 IU/kg 3 times a week	20	50	35	156	156	156	3,120	7,800	5,460
	20-40 IU/kg every 2 days	20	40	30	183	183	183	3,650	7,300	5,475

Table I. *Annual average consumption per patient of the available treatments, base on European SPCs [12,15,18-25].*

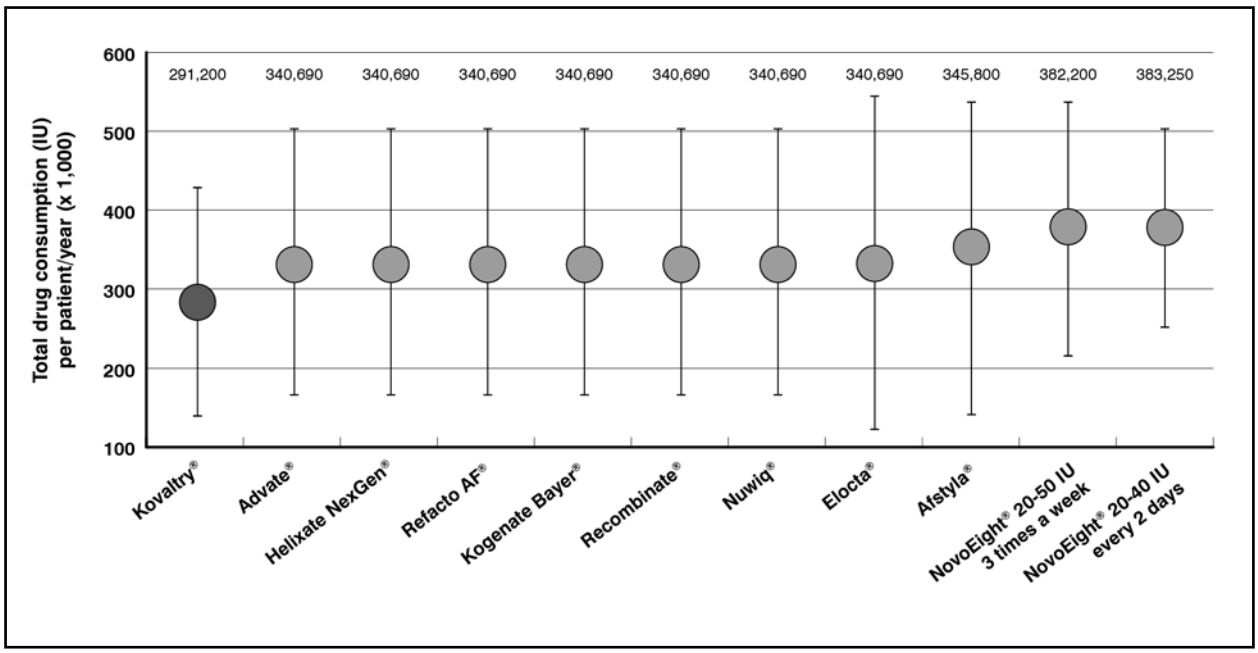

Figure 1. *Annual average drug consumption (IU) for a 70 kg patient (including min-max)*

administrations/year without increasing the unitary dosage per administration. Considering average dosages per year of Kovaltry® and competitors (reported in SPCs [12,15,18-25]), all therapies are associated with higher drug consumption versus Kovaltry:

- Standard therapy (Advate®, Helixate NexGen®, Recombinate®, Kogenate®, Refacto AF®, Nuwiq®) = +17%;
- Novoeight® = +31%, +32%;
- Elocta® = +17%;
- Afstyla® = +19%.

The potential benefit in terms of drug consumption reduction will be further evaluated in real life condition according to current clinical practice. As in Italy the rFVIII are acquired by NHS facilities through tenders, the annual cost was estimated considering the average selling prices to NHS structures [26-38]. As Afstyla® has been very recently reimbursed and no data on real selling price (i.e. Regional determinations or NHS structures tenders) are available, even if approved price per IU is higher than the average selling pri-

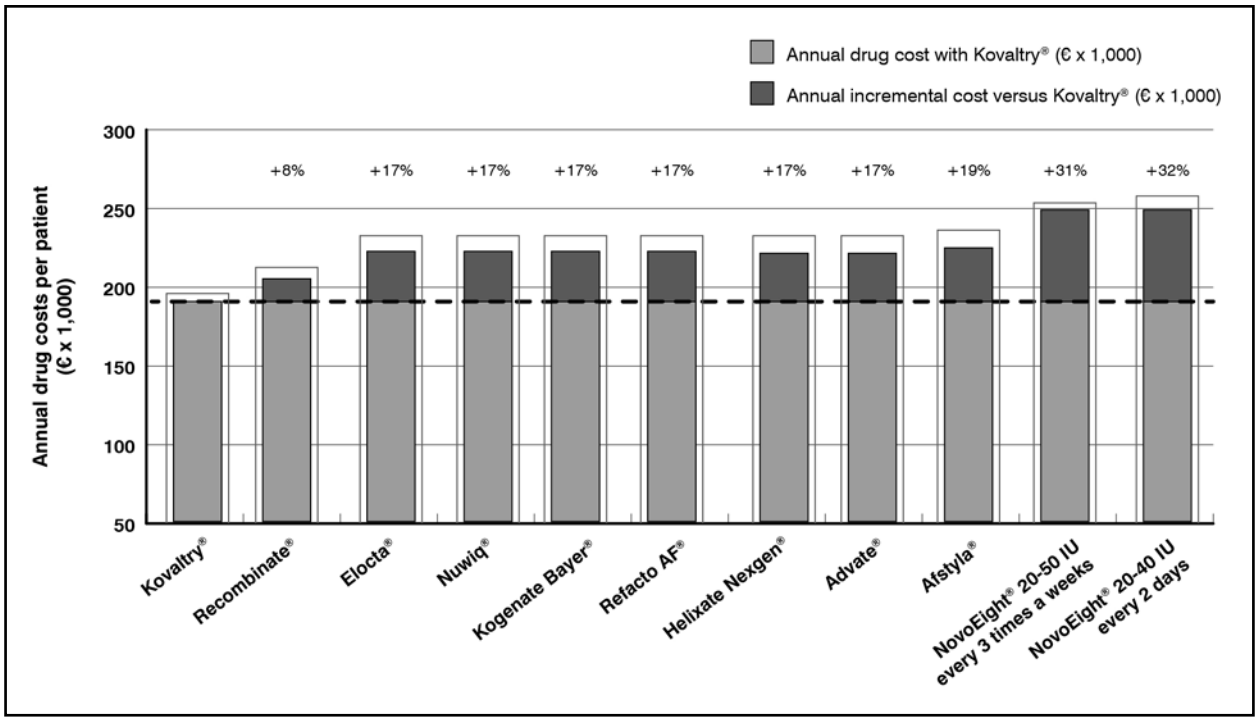

Figura 2. *Average annual costs per patient (70 kg weight) for the approved drugs*

ces of other rFVIII, we have conservatively estimated the average annual cost per patient considering the same price per IU (0.65 €) of the other rFVIII (excluding Recombinate® which has a net selling price of 0.60 €/IU).
As highlighted by the Figure 2, at average dosages reported in SPCs [12,15,18-25], all the competitors result to be more expensive than Kovaltry® on a yearly bases with incremental costs ranging from about +15,000 €/year (+8% for Recombinate®) to +60,000 €/year (+32% for NovoEight®). Elocta®, at average dosage (45 IU/kg) leads to an incremental cost of about € 32,000 (+17%) versus Kovaltry®. The last marketed rFVIII, Afstyla® at average dosage (35 IU/kg) leads to an incremental cost of about 35,500 € (+19%) versus Kovaltry®.

The estimates of average consumptions and related costs of the different rFVIII reported in the present analysis, are based on dosages/frequence of administration reported in the European Summary of Product Characteristics and clinical trials and should be confirmed through real world observations.
However, an approach that has the potential to reduces the number of administrations per year without any increase in dosage, as is proposed for Kovaltry®, can potentially improve patient quality of life and faciliate compliance to treatment as well as produce potential savings for the Italian NHS thanks to the reduction of rFVIII utilization and a reduction in costs related to a lower risk of breakthrough bleedings and the related complications.

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