The increased demand for plasma-derived factor VIII in Italy between 2011 and 2014 is attributable to treatment of adult patients rather than paediatric or previously unexposed patients with severe haemophilia A

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Dear Sir,

Arcieri and Colleagues[1] recently discussed the increasing demand for plasma-derived factor VIII (FVIII) concentrates to treat people with haemophilia A recorded in Italy between 2011 and 2014. Requests for plasma-derived FVIII reached about 27% of the total FVIII demand, with a 58% increase[2]. As possible explanations, they identified broader implementation of immune tolerance induction with von Willebrand factor-containing plasma-derived products in poor-prognosis patients, or the switch from on-demand to prophylactic regimens in adult/elderly patients, receiving plasma-derived FVIII, due to co-morbidities and drugs (antiplatelet and anti-inflammatory agents) increasing bleeding risk. However, they also highlighted the changing perception in Italian patients and physicians about plasma-derived products, i.e. an increased awareness of their pathogen safety, the advantages in economic sustainability and, moreover, the perceived lower immunogenicity in previously untreated patients, which may have influenced the choice in patients at high risk of inhibitor formation. Overall, they considered this trend in FVIII demand as discrepant with the recommendations published by the Italian Association of Haemophilia Centres (*Associazione Italiana Centri Emofilia*, AICE) in 2014[3], which leave a role for plasma-derived FVIII in a minority of patients, and indicate recombinant FVIII concentrates as the products of choice for previously untreated patients, minimally treated and previously treated patients exposed exclusively to recombinant products, human immunodeficiency virus-positive patients with overt signs of immune deficiency and previously treated patients exposed to plasma-derived concentrates but not infected by (or who have cleared) hepatitis C virus. The authors, therefore, envisaged a revision of the AICE recommendations, in particular in the light of the recent results of the Survey of Inhibitors in Plasma Product Exposed Toddlers (SIPPET) study, confirming a reduced inhibitor rate in previously untreated patients treated with plasma-derived FVIII compared with recombinant products[4].

The increased demand for plasma-derived FVIII should be evaluated in the frame of the overall higher demand for FVIII products in Italy, which rose from 6.5 to 9.0 IU per capita in the 3-year period under consideration. In this scenario, recombinant FVIII consumption also increased by 33%[2]. Together with longer life-expectancy and general improvement of treatment, the growing demand for FVIII products can be explained by the more widespread adoption of immune tolerance induction and prophylactic regimens, prompted by intense clinical research on outcomes carried out in Italy and abroad[3]. According to the National Registry of Congenital Coagulation Disorders, jointly held by the Italian National Institute of Health and AICE, 44 subjects were undergoing immune tolerance induction in 2014[5], with a remarkable increase from the 24 patients in 2011. In particular, there was a relevant proportion of adolescents and adults on immune tolerance induction (7 patients were between 10 and 20 years old, 10 were older than 20 years)[5], in most cases (>70%) treated with plasma-derived products, with an overall increase from 42 to 59% of the total FVIII used for immune tolerance induction (Hassan, *personal communication*). As far as concerns the diffusion of prophylaxis, the National Registry recorded that the percentages of patients with severe haemophilia A on prophylaxis were 71% in 2011 and 77% in 2014[5]. Interestingly, alongside the use of primary prophylaxis in children, tertiary prophylaxis in adolescents and adults has been increasingly adopted[3]. Both these therapeutic approaches had a greater impact on the consumption of plasma-derived FVIII, due to its use in adult patients, as mentioned by Arcieri and Colleagues[1]. In our opinion, these reasons are sufficient to explain the increased demand for plasma-derived FVIII, whereas the use in previously untreated patients is unlikely to play a role. In the 2013 survey, the Directors of AICE Centres almost unanimously (95%) indicated recombinant concentrates as the recommended products for previously untreated patients[3]. Furthermore, fewer than 20 neonates with severe haemophilia A are registered every year in Italy[5] and, taking into account their body weight, the FVIII use in this subgroup of patients has a negligible impact on the national FVIII consumption.

[1]The full affiliations of the Members of the AICE Council are listed in the Appendix

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The AICE Principles of Treatment were updated in 2014 in order to take into account the results of large prospective studies and a systematic review and meta-analysis of literature in which no difference in inhibitor risk between plasma-derived and recombinant FVIII products was shown[3]. This AICE document stated a basic principle that should drive the decisional process regarding the choice of the type of product to give to previously untreated patients, as well as to all people with haemophilia and other congenital bleeding disorders, i.e. accurate information and thorough discussion with the patient or his/her parents about all the available options and literature data supporting their efficacy and safety, including still debated issues[3]. Such active involvement is crucial for taking a shared decision and obtaining the patient's or parents' informed consent to treatment with a specific product.

Along this line, AICE doctors already inform parents of newly diagnosed children with severe haemophilia A of the important results from the randomised SIPPET study in previously untreated patients[4], together with all other available information, when jointly taking the decision on which FVIII product to administer for replacement treatment. This approach will continue to work and build the therapeutic alliance between patients and doctors, irrespectively of the changing scenario of replacement products (newer FVIII concentrates not evaluated in the SIPPET study), the study results and the updates of recommendations, currently planned by AICE every three years.

Disclosure of conflicts of interest

AC has received fees as an invited speaker or consultant from Baxter, Bayer, NovoNordisk and Octapharma. ES has acted as a paid consultant or invited speaker for Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Kedrion, NovoNordisk, Octapharma, Pfizer, Roche and Sobi, and has received an unrestricted research grant from Pfizer; ACM has received fees as an invited speaker or a member of advisory boards from Bayer, CSL Behring, Kedrion, NovoNordisk, Pfizer and Sobi; RCS has received fees as an invited speaker or member of advisory boards from Baxalta, Bayer, BioVIIIx, Boehringer Ingelheim, Bristol-Myers-Squibb, CSL Behring, Pfizer, Sanofi-Aventis and Sobi; AT has acted as a member of an advisory board or consultant for Baxter, Bayer, CSL Behring, NovoNordisk, Pfizer and Sobi; MM has acted as a paid consultant or invited speaker for Baxter, Bayer, CSL Behring, NovoNordisk, Octapharma and Pfizer, and has received research grants from Baxter, Bayer and Pfizer. GDM has acted as a consultant or ad hoc speaker for Bayer, Boehringer Ingelheim, Biotest, CSL Behring, Eli Lilly, Grifols, NovoNordisk, Pfizer and Sanofi-Aventis. HJH declared no conflicts of interests.

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Appendix

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