In reply

Factor VIII inhibitor and source of replacement therapy

Pier Mannuccio Mannucci[1], Alessandro Gringeri[2], Elena Santagostino[2], Flora Peyvandi[2]

[1]Scientific Direction; [2]Hemophilia and Thrombosis Centre, A. Bianchi Bonomi, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy

Dear Sir,

In their timely letter on the current state of haemophilia therapy, Calizzani and Arcieri[1] tackle two clinically important points: the effect of the source of factor VIII replacement therapy (plasma-derived or recombinant) on the cumulative incidence of factor VIII inhibitors in patients with haemophilia A; and whether or not the so-called continuity of care with the very coagulation factor product to which patients are accustomed is warranted.

As to the first point, and pertaining to the debate between Franchini[2] and Mannucci[3] and the article by Gringeri[4] on the choice of factor VIII products, Calizzani and Arcieri must be reassured that the forthcoming therapeutic recommendations of the Italian Association of Haemophilia Centres (AICE) on the choice of products for replacement therapy will be strictly based on the available scientific evidence. A recent systematic review and meta-analysis found a two-fold increased incidence of inhibitors associated with the use of recombinant factor VIII[5], but the difference in favour of plasma-derived factor VIII lost its statistical significance when important variables such as study design, study period and frequency of inhibitor testing were tested as confounders[5]. Hence, there is a state of uncertainty on the effect of the source of factor VIII on inhibitor incidence. This state of uncertainty (clinical equipoise) is the justification for our decision to organise the currently ongoing randomized SIPPET study[6].

Debates such as those published in this journal[2,3] and other journals on different competing therapies inevitably lead the "duelists" to defend vigorously one position, and only that one. We are indeed convinced that the available data do justify the design of the SIPPET study[6], based on the hypothesis of a lower incidence of inhibitors in patients treated with plasma-derived, von Willebrand factor-containing factor VIII products. Yet, we are also cognizant that this is a working hypothesis, not yet evidence-based: otherwise the SIPPET study would be unnecessary!

Pertaining to the so-called continuity of care, we agree with Calizzani and Arcieri that this should be preserved as much as possible. However, the issue is not that switching from one source and/or product of factor VIII to another would increase the risk of inhibitor. There is so far evidence that switching from a plasma-derived to a recombinant product or, by the same token, from a recombinant product to another does not increase inhibitor incidence in previously treated people with haemophilia[7-9]. For plasma-derived factor VIII the only study showing, albeit indirectly, that changing products leads to a higher cumulative incidence of inhibitors stems from the systematic review of Paisley *et al.*[10], with a number of other studies showing that switching is neutral in this respect[7-9]. Nevertheless, some large cohort studies are ongoing in Europe and in the UK (for instance, C. Hay, communication at the 7th Bari International Conference, Pugnochiuso, Vieste del Gargano, Italy, 21-23 May 2011), which, it is to be hoped, will provide a definitive answer. While waiting for the still unavailable evidence that haemophilia care can be personalised[11], we are in favour of continuity for a different but very important reason: the need for a robust pharmacovigilance system. Even though all anti-haemophilic products have currently reached an unprecedented level of safety, pharmacovigilance is still essential, as exemplified by the action taken by the European Association of Haemophilia and Allied Disorders together with the European Haemophilia Consortium in developing and fostering the EUHASS project[12]. Pharmacovigilance is also rendered cogent by the ongoing developments in DNA technology, which, it is to be hoped, will soon make available factor VIII and factor IX products

with an extended plasma half-life[13]. The long-term safety of these products, and the current theoretical concerns on conjugate tolerogenicity and neo-epitope immunogenicity can only be firmly established by pharmacovigilance programmes such as EUHASS. Most importantly, we learnt a lesson from the 1980s drama of human immunodeficiency virus and hepatitis C virus infections. At that time the limited availability of coagulation factor products, which often forced us to change products, made it difficult to identify the lots and products carrying a higher risk of viral infections. Another potential reason for supporting the so-called "continuity of care" is compliance, which can be jeopardised by frequent switching among different products.

Conflict of interest

Pier Mannuccio Mannucci has received fees for consultancy and participation as a speaker at scientific meetings organised through unrestricted educational grants from producers of plasma-derived coagulation factor concentrates (Kedrion, Grifols), as well as by manufacturers of recombinant factor VIII (Baxter, Bayer, Pfizer).

Alessandro Gringeri has received unrestricted research grants from producers of plasma-derived (Biotest, CSL Behring, Grifols, Talecris) and recombinant coagulation factor concentrates (Baxter, CSL Behring, Pfizer), fees for consultancy from a manufacturer of recombinant factor VIII (Baxter), and fees for participation as a speaker at scientific meetings by producers of both plasma-derived coagulation factor concentrates (Biotest, Grifols, Octapharma) and recombinant factor VIII (Baxter, CSL Behring, Novo Nordisk).

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Correspondence: Pier Mannuccio Mannucci
Scientific Direction
IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation
Via Pace 9
20122 Milano, Italy
e-mail: piermannuccio.mannucci@unimi.it