LETTER TO THE EDITOR

Switching to extended half-life products in Canada – preliminary data

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Two extended half-life (EHL) recombinant factor concentrates, Alprolix (rFIX-Fc) and Eloctate (rFVIII-Fc; both from Biogen, Missisauga, Ontario, Canada) were approved in 2014 by Health Canada for use in patients ≥12 years of age with FIX (haemophilia B) and FVIII deficiency (haemophilia A) respectively. Both products became available outside the province of Quebec in February 2016 through Canadian Blood Services (CBS) with criteria for use established by the National Advisory Committee on Blood and Blood Products (NAC; www.nacblood.ca). This report summarizes Canadian utilization data for the first 8 months following the availability of these products. In this same time period, a national tender resulted in one standard half-life (SHL) rFVIII (at the time used by about half the number of all patients with severe haemophilia A) no longer being available requiring patients on this product to switch to another FVIII. We believe the experience of switching factor products in Canada might be of value for other countries or centres planning to adopt EHL products into clinical practice.

The data for this report was collected by means of the Canadian Bleeding Disorder Registry (CBDR, available at www.cbdr.ca), a database of Canadian patients with bleeding disorders operated by the AHCDC. For those haemophilia treatment centres (HTCs) not yet using CBDR, data was supplemented with directly sourced information. In such cases, data were extracted from medical records and paper diaries submitted by patients and aggregated as required.

Relevant information was obtained for 139 patients from 15 centres located in eight Canadian provinces. Of these 139 patients who switched, 105 (76%) had severe haemophilia A, 24 (17%) had severe haemophilia B, four (3%) had moderate haemophilia A and six (4%) had moderate haemophilia B. Of the 139 patients who switched to an EHL factor concentrate, 109 (79%) switched to Eloctate and 30 (22%) to Alprolix; 69% were <18 years of age (54% of these were from a single centre), 14% were between 18 and 35 and 17% were >35 years of age. We retrieved treatment logs and/or treatment plans for 127 patients, of whom 95% were on prophylaxis pre-switching, 4% were switched from on demand to prophylaxis and only one continued on demand with the EHL product. The reported reason for switching, coded according to the NAC criteria, was ‘to improve quality of life’ for 70% of patients and ‘to improve compliance’ in 16%; 8% of patients were switched with the goal of decreasing the frequency of bleeds occurring on prophylaxis with SHL products.

In severe haemophilia B, median weekly dose kg⁻¹ for Alprolix was 53 International Units (IU) with a range between 42 and 94 IU, and an IQR of 12. In severe haemophilia A, median weekly dose kg⁻¹ for Eloctate was 82 IU, ranging between 36 and 140 IU with an IQR of 28. Complete utilization data were retrieved for the 6 months preceding the switch from 86 patients (96% on prophylaxis prior to switching), reporting a total utilization of 11 537 966 IU of SHL

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concentrates, corresponding to an average of 134 162 IU per patient over a period of 6 months. EHL factor utilization was projected for these patients based on their initial prescribed doses to be a total of 7 805 999 IU at an average of 90 767 IU per patient over 6 months; this represented an average decrease per patient of 43 395 IU. A patient on immune tolerance induction (ITI) using Eloctate was excluded from these calculations. Patient weight was available for 79 of the 86 patients allowing us to calculate IU kg\(^{-1}\) week\(^{-1}\) usage. The Table 1 shows a breakdown of the 79 cases with 6 months pre- and post-switch factor utilization by IU kg\(^{-1}\) week\(^{-1}\) and is derived mostly from paediatric patients from one centre (52/79, 66%). This shows that on a IU kg\(^{-1}\) week\(^{-1}\) basis patients transitioning to EHL rFVIII-Fc from SHL rFVIII reduced their factor utilization by 19% while patients transitioning to EHL rFIX-Fc from SHL rFIX reduced their factor utilization by 50%. Data from one large paediatric program indicates that 45 children with severe haemophilia A reduced the number of infusions per week from an average of 3 to 2, a decrease of one infusion per week per patient. Within the same centre, seven children with severe haemophilia B reduced the average number of infusions per week from 2.5 to 1.

No development of inhibitors was observed via the CHESS (Canadian Hemophilia Safety Surveillance) programme following the switch, although the follow-up period is relatively short.

In conclusion, this is the first experience with marketed EHL products in Canada and represents the early utilization and switching patterns observed. Many switches from SHL to EHL products occurred in paediatric haemophilia A patients who were already on prophylaxis and were required to switch as a result of a national tender resulting in one SHL rFVIII being no longer available. This created a situation where patients on one specific SHL FVIII product may have been more likely to switch to an EHL than patients on other SHL FVIII products. All patients were educated about all available FVIII products so that they could make an informed decision from among all available options. However, it is possible that unavoidable variability in patients and clinicians’ discussions and preferences around product switch might explain differences in behaviour and switching rates in subpopulations across the country. Decisions regarding patients under 12 years of age were largely taken by their parents, while older children were progressively more involved in providing their own input towards the decision. As per NAC criteria, improving quality of life was by far the most frequent reason to switch – in 70%. Improving quality of life can of course be accomplished in different ways – by decreasing the frequency of infusions or by increasing the target trough factor level thereby allowing the patient to be more active without increased risk of bleeding. Given that most patients opted for less frequent infusion schedules, we presume that the primary motivator to switch to EHL factor concentrates was likely the former (reducing infusions) and not as likely the latter (increasing trough levels).

This preliminary data focused exclusively on utilization and prescribing practices. Further data collection with CBDR is ongoing that will include clinical end points (bleeding episodes and measured trough levels) and health outcomes in future reports to provide a more complete picture of the utility and impact of EHL products in the Canadian bleeding disorders population.

### Disclosure

V Bousskill has received honoraria for advisory board participation with Bayer HealthCare, Biogen, CSL Behring, Novo Nordisk, Octapharma, and Pfizer; and for speaking for Biogen. M Carcao has received research funding from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, Novo Nordisk and Pfizer; additionally, he has received honoraria for advisory board participation and for speaking from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, Biotest, CSL Behring, Novo Nordisk, Octapharma, and Pfizer. He is a principal investigator on a Biogen rFVIII-Fc PUP study. J Stoffman is a consultant for Bayer Inc. A Iorio’s Institution has received project based funding via research or service agreements with Bayer, Novo Nordisk, Pfizer and Shire (formerly Baxter and Baxalta).

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<th>Severe haemophilia A (n = 62)</th>
<th>Severe haemophilia B (n = 17)</th>
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<tbody>
<tr>
<td><strong>Median, (IQR)</strong></td>
<td><strong>IU kg(^{-1}) week(^{-1})</strong></td>
<td><strong>IU kg(^{-1}) week(^{-1})</strong></td>
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<tr>
<td>Pre-switch</td>
<td>101 (70; 115)</td>
<td>105 (64; 146)</td>
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<tr>
<td>Post-switch</td>
<td>82 (70; 98)</td>
<td>53 (48; 60)</td>
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<tr>
<td>Change</td>
<td>-19%</td>
<td>-50%</td>
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<tr>
<td><strong>Range (IU kg(^{-1}) week(^{-1})</strong></td>
<td>-200 – 12</td>
<td>46 – 235</td>
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<td>36 – 140</td>
<td>42 – 94</td>
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\(^*\)76/79 of these cases on prophylaxis prior to switching.