

Adult severe haemophilia A patients under long-term prophylaxis with factor VIII in routine clinical practice

María E. Mingot-Castellano^a, Laura González-Díaz^a, Rocio Tamayo-Bermejo^b and Anabel I. Heiniger-Mazo^a

There is no clear consensus on the best practice for long-term prophylaxis in adults with severe haemophilia A. This is a single-centre prospective case series study. We describe here the demographic data, type and reason of prophylaxis in adult patients (>18 years old) with severe (<1%) haemophilia A, treated in our centre from 2006 to 2013. Prophylaxis was tailored according to pharmacokinetic studies and posterior factor VIII (FVIII) trough level adjustment. We analysed FVIII consumption, bleeding rate, adherence and adverse events in this group of patients. In adult patients who initiated long-term prophylaxis during this period, we compared FVIII consumption and bleeding rate with the previous on-demand period. We analysed data from 18 patients. Median annual FVIII consumption was 2374.2 IU/kg/year. Among the patients receiving tertiary prophylaxis, initiated from 2006 onwards, the annual FVIII consumption was 2557.8 vs. 1696.8 IU/kg per year during the on-demand period ($P = 0.312$). In this group of patients, there was a decrease in annual bleeding events of 88.3% during prophylaxis compared with the on-demand therapy ($P < 0.0001$). A high adherence to prophylaxis was observed (84%). No cases of anaphylaxis or symptomatic thromboembolic events were recorded. In adult severe

haemophilia A patients, the type of and reason to indicate long-term prophylaxis are diverse nowadays. FVIII consumption varies depending on the justification of prophylaxis. The observations reported provide further support for the efficacy of long-term prophylaxis in adult haemophilia A patients. *Blood Coagul Fibrinolysis* 26:000–000 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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^aHematology Department and ^bPharmacy Department, Regional University Hospital of Malaga, Malaga, Spain

Correspondence to Maria Eva Mingot-Castellano, PhD, Haematology and Haemotherapy Clinical Department, Regional University Hospital of Malaga, Malaga, Spain
Tel: +34 951 291 168; fax: +34 951 291 168; e-mail: maria.e.mingot.sspa@juntadeandalucia.es

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Introduction

Patients with severe haemophilia A generally require prophylactic replacement therapy in order to prevent spontaneous bleeding and haemophilic arthropathy [1–3]. Long-term prophylactic replacement therapy with factor VIII (FVIII) is widely accepted for children and has been recommended by both the WHO and the World Federation of Haemophilia (WFH) [3,4]. These recommendations were supported by the results of an early case series and longitudinal studies that demonstrated reductions in bleeding events and stabilization of arthropathy in children with severe haemophilia managed with continuous prophylaxis [5,6].

In 2001, the National Haemophilia Foundation adopted the recommendation of the Medical and Scientific Advisory Council (MASAC) for prophylaxis as the optimal treatment for patients of any age with severe haemophilia [7]. Adult patients with severe haemophilia A have been traditionally treated on demand, and almost all of them present haemophilic arthropathy. It seems that prophylaxis is not able to recuperate normal joint status, but could delay arthropathy progression. Despite this, the lack of controlled studies makes it difficult to assess the

benefits of starting prophylaxis in adolescent or adult haemophilia patients.

In 2010, Collins *et al.* [8] published the results of the first prospective study designed to compare the efficacy of on-demand vs. prophylaxis schemes of treatment in adults. A total of 20 patients between 30 and 45 years old with severe haemophilia A participated in a 13-month prospective, cross-over, open-label study. A reduction in the incidence of haemarthrosis and an improvement in joint function were observed during the prophylaxis period compared with the on-demand period. Most recently, first-year results of the SPINART study provide further support for the benefits of prophylactic vs. on-demand treatment in adults with severe haemophilia A [9]. This randomized and open-label study describes a significant reduction in total bleeding events (median number of events during prophylactic treatment 0 vs. 54.5 during on-demand treatment; $P < 0.0001$) [9].

At present, there is no clear consensus on the best practice for long-term prophylaxis treatment in adults with severe haemophilia A with regard to indications, dosing and management [10,11]. We present the results

of long-term prophylaxis schemes of treatment in adult patients with severe haemophilia A. We describe patient profiles, reasons to indicate prophylaxis, type of prophylaxis and the protocol to individualize the prophylaxis scheme. We describe efficacy and safety of prophylaxis and compare them with on-demand treatment in patients under tertiary prophylaxis. Adherence and FVIII adverse events were also analysed.

Materials and methods

Study design

We performed a prospective case series study to describe and to evaluate efficacy and safety of long-term prophylaxis in routine clinical practice in adult patients (over 18 years old) with severe haemophilia A (FVIII less than 1%). We included patients on long-term prophylaxis treated in our centre from January 2006 to December 2013 – both patients under long-term prophylaxis since childhood and adult patients in whom prophylaxis is indicated for the first time.

Patients with active inhibitor or antecedents and those with a concomitant bleeding disorder were excluded. The study was conducted according to the Declaration of Helsinki and was approved by the Research Committee of the Regional University Hospital of Malaga (Malaga, Spain). All patients provided written informed consent to be included in the study and for the confidential use of their medical records for research purposes.

Treatment

From 2006 onwards, we indicated almost one pharmacokinetic study to adjust dose and frequency of long-term prophylaxis in every severe haemophilia A patient over 18 years old treated in our adult patient centre. Pharmacokinetic studies were based on the recommendations by Shapiro *et al.* [12]. We defined a washout period of 72 h. We determined baseline FVIII levels. Then, 50 IU/kg of FVIII were infused, and 30 min later, a blood sample was collected to define the patient's recovery. Pharmacokinetic study was performed using this information and another five to eight points, with blood samples collected between 6 and 48 h after FVIII administration. Samples were extracted by antecubital venipuncture into citrate tubes and processed within 1 h of extraction. FVIII levels were determined using a one-stage method.

Prophylaxis dose and frequency were designed according to the pharmacokinetic results. After this, patients were reviewed every 2 months to adjust prophylaxis to FVIII trough level of between 1 and 3%, with no more than one spontaneous bleeding event every 2 months, or no more than two events every 6 months in the same joint. We chose this target based on the study by Aznar *et al.* [13], who published good results using these trough levels, and the recommendations by Collins *et al.* [14]. After prophylactic dose stabilization, patients were reviewed every 6 months.

The on-demand FVIII replacement regimens used in our clinic in case of bleeding for on-demand patients or for bleeding events in patients under prophylaxis were 10–25 IU/kg for mild events or 25–50 IU/kg for moderate events every 12–24 h for 1–3 days until the bleeding episode was solved [3]. For major bleeding events, patients received 30–60 IU/kg every 8–12 h until the bleeding episode ceased [3].

Data collection

On inclusion in the study, data collected were patient demographics, date of diagnosis of haemophilia A, genetic abnormalities, date of initiating current prophylaxis, type and reason to start long-term prophylaxis and target joints. Prophylaxis has been classified according to WFH criteria [3]. Joint damage to define tertiary prophylaxis was defined using clinical criteria (Gilbert) [3] and radiologic criteria (Petterson score) [15]. Target joints at the start of prophylaxis were defined as a joint with four or more haemorrhages in the past 6 months or more than 20 in total [16].

Patients' records on FVIII infusions and bleeding events were reviewed every 6 months. In those patients who initiated long-term prophylaxis from 2006 onwards, we retrospectively recorded FVIII consumption and bleeding events from the year before the inclusion in the prophylaxis program to compare long-term prophylaxis efficacy.

In addition, information on adherence to treatment and the reason for any lack of adherence was collected using haemophilia diaries routinely completed by patients. Adherence was calculated as a percentage (number of weeks during the year with the correct number of prophylaxis infusions/number of weeks during the year without surgery or bleeds needing haemostatic treatment with FVIII). Hospitalization, anaphylaxis, ischaemic or venous thrombosis events were recorded.

Statistical analyses

A descriptive analysis was performed, using absolute and relative frequencies for qualitative variables, and centralization and dispersion measures for continuous variables: number of non-missing observations, mean, SD, median, inter-quartile range (IQR Q1–Q3), minimum and maximum.

Pearson's chi-square test (or Fisher's exact test for 2 × 2 tables) was used to find the relationship between qualitative variables. The Student's *t* test or analysis of variance (ANOVA) was used for the comparison of continuous variables, if parametric criteria were fulfilled. On-demand treatment and prophylaxis were compared using unpaired *t* test. Otherwise, non-parametric tests were used. A 0.05 two-sided significance level was considered to indicate statistical significance throughout.

Table 1 Demographics and medical history of the study population

Parameter	Patients with severe haemophilia A treated with prophylactic factor replacement (<i>N</i> = 18)
Age at diagnosis [months, median (IQR)]	6.5 (2.5–12.0)
Height [cm, median (IQR)]	176.0 (173.5–180.5)
Weight [kg, median (IQR)]	84.5 (74.3–92.5)
BMI [kg/m ² , median (IQR)]	26.4 (24.3–29.2)
Reason for initial diagnosis [<i>n</i> (%)]	
Family history	5 (27.8%)
Cephalohematoma (forceps delivery)	1 (5.6%)
Traumatic retroocular haematoma	1 (5.6%)
Haematoma after vaccination	2 (11.1%)
Muscular haematoma	2 (11.1%)
Abnormal equimosis	7 (38.9%)
Presence of genetic mutation [<i>n</i> (%)]	
Inversion (intron 22)	5 (27.8%)
Substitutions and deletions	13 (72.2%)
Immune status [<i>n</i> (%)]	
HCV	6 (33.3%)
Co-infections HIV and HCV	8 (44.4%)
HCV and HIV negative	4 (22.3%)
Inhibitor history [<i>n</i> (%)]	
Low titre (low responder)	6 (33.3%)
Haemophilic arthropathy [<i>n</i> (%)]	15 (83.3%)
Affected joints [<i>n</i> (%)]	
Knee	10 (55.6%)
Elbow	7 (38.9%)
Ankle	5 (27.7%)
Shoulder	3 (16.7%)

BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, inter-quartile range (Q3–Q1).

Results

A total of 18 individuals have been evaluated. Table 1 provides an overview of the characteristics of the study population.

Prophylaxis description

The majority of patients (16/18; 88.9%) received recombinant FVIII (rFVIII). Only two patients were treated with plasma-derived FVIII (pdFVIII). The median age at the start of prophylaxis was 30 years (IQR 17.0–40.5 years).

Two patients were under primary prophylaxis, two under secondary prophylaxis and 14 (77.8%) received tertiary prophylaxis. All the patients under tertiary prophylaxis started long-term prophylaxis during adulthood, from 2006 onwards. The median age at tertiary prophylaxis was 31.5 years (IQR 22–71 years). The reasons to indicate tertiary prophylaxis included frequent haemarthrosis and worsening of haemophilic arthropathy (11/14), central nervous system haemorrhage (2/14) and need of antiplatelet drugs because of stroke (1/14).

Individual patient FVIII doses were calculated on the basis of the pharmacokinetic study, number of bleeds and trough levels. The mean volume of distribution (Vd), terminal half-life ($t_{1/2}$) and clearance (Cl) were 51.1 ± 6.0 ml/kg, 13.2 ± 5.8 h and 3.0 ± 1.0 ml/kg, respectively. The prophylaxis dose frequency indicated was twice a week (8/18 patients), three times a week (7/18 patients) or every 48 h (3/18 patients). After the first 2 months, no increase in treatment was necessary. Five patients presented trough values higher than 3% without

bleeds. According to our protocol, dose or frequency was reduced to get a trough FVIII level between 1 and 3%. For three patients, the dose frequency was reduced from three times to twice a week. The other two patients decreased the FVIII units per dose. After these trough FVIII level adjustments, no increase in haemorrhagic events was observed and prophylaxis modifications were not required. Thanks to the final trough level adjustments in this group of five patients, the FVIII consumption was statistically reduced by 31.3% (mean monthly FVIII consumption 298.3 ± 101.5 vs. 203.5 ± 67.0 IU/kg; $P = 0.004$).

Annual factor VIII consumption

For all patients, the annual FVIII consumption was 2374.2 IU/kg per year (IQR 1662.0–3088.2 IU). In adult patients, receiving tertiary prophylaxis (14 patients), the annual FVIII consumption was 2557.8 IU/kg per year (IQR 1662.0–3217.5 IU), representing an increased FVIII consumption of 50.7% compared with the on-demand consumption during the year before the inclusion in the prophylaxis program [1696.8 IU/kg per year (IQR 1022.1–3312.0 IU/kg per year); $P = 0.312$]. In this group of patients, we analysed those that initiated tertiary prophylaxis due to frequent haemarthrosis and worsening of joint performance (11 patients). The annual FVIII consumption was 2535.6 IU/kg per year (IQR 1500.0–3366.0 IU) during prophylaxis and 1713.6 IU/kg per year (IQR 1250.4–3108.0 IU/kg per year) during the previous on-demand period ($P = 0.494$). This equated to an increased annual FVIII consumption of 24.5%. Table 2 provides an overview of the time on prophylaxis

Table 2 Factor VIII consumption during on-demand and tertiary prophylaxis

	All patients (N = 18)	Tertiary prophylaxis patients (N = 14)		Patients switched to tertiary prophylaxis due to haemarthrosis (N = 11)		
Median month in prophylaxis (IQR)	23.0 (15.0–57.0)	21.0 (15.0–49.8)		19.0 (12.0–72.0)		
		During a previous on-demand period	During tertiary prophylaxis	P	During a previous on-demand period	During tertiary prophylaxis
Median annual bleeding rate (IQR)		21 (10.5–23.5)	2 (0–4)	0.0001	21 (17–25)	2.5 (0.25–4)
Median yearly/kg FVIII consumption (IU/kg/month) (IQR)	2374.8 (1662–3088.2)	1696.8 (1022.1–3312)	2557.8 (1662–3217.5)	0.312	1713.6 (1250.4–3108)	2535.6 (1500–3366)
						P
						0.0001
						0.494

FVIII, factor VIII; IQR, inter-quartile range (Q3–Q1).

and the FVIII consumption during prophylaxis and on-demand treatment for patients under tertiary prophylaxis.

Annual rate of bleeding events

For all patients, the median annual rate of bleeding events was 2 (IQR 0–3, 25). Among the 14 patients receiving tertiary prophylaxis, the median annual bleeding event rate was 2 (IQR 0–4) during prophylaxis and 21 (IQR 10.5–23.5; $P < 0.0001$) during the on-demand period. There was a decrease in annual bleeding events of 88.8% during prophylaxis. In patients under tertiary prophylaxis to prevent haemophilia arthropathy progression, the median annual bleeding event rate declined from 21 (IQR 17–25) during on-demand treatment to 2.5 (IQR 0.25–4; $P < 0.0001$) during prophylaxis (see Table 2).

Most bleeds during prophylaxis were haemarthrosis, 82% of them being traumatic. There were no new target joint during prophylaxis follow-up. Between no joint bleeds, we reported two spontaneous and three traumatic muscular haematomas. The patient under anti-platelet therapy suffered from two episodes of digestive haemorrhage with mild haemoglobin decrease and was managed as an outpatient.

Adherence

Median adherence to prophylaxis was 84.0% (IQR 69.0–96.0%). During regular evaluations, patients associated poor adherence to active working lives and irregular work schedules. Adherence was similar between patients treated with primary or secondary prophylaxis and those who received tertiary prophylaxis [85.0% (IQR 73.0–96.0%) and 83.0% (IQR 69.0–95.0%), respectively].

Adverse events

No cases of anaphylaxis or symptomatic arterial ischaemia or thromboembolic events were recorded. No surgeries were performed during the follow-up time.

Discussion

The present prospective case series of 18 adult patients with severe haemophilia A treated in our clinic under prophylaxis treatment schemes supports the concept that even in patients with established haemophilic arthropathy, prophylaxis is an appropriate option to reduce the rate and

burden of bleeding events. In the four patients under primary and secondary prophylaxis, continuing these treatment schemes, and not stopping due to adulthood, could be the key to maintaining optimal joint status.

Prophylaxis efficacy in this cohort of patients, in terms of reduction in bleeding rate, is consistent with the previously reported data in adolescent and adult patients with severe haemophilia A [17,18]. The SPINART study [9] – a randomized, parallel-group, controlled trial of routine prophylaxis vs. on-demand treatment in 84 patients with severe haemophilia A – has shown that routine prophylaxis significantly reduced bleeding compared with on-demand factor replacement. The annual number of bleeds declined from 27.9 to 0.0 under prophylaxis ($P < 0.0001$) [9]. This was comparable to the 88.8% reduction observed in our case series. In 2011, Collins *et al.* [8] reported the results of a 13-month cross-over study, comparing the efficacy and safety of secondary prophylaxis and on-demand therapy in 20 patients with severe haemophilia A. In this study, the reduction in bleeding events was comparable with that observed in previous studies and in our data. The mean annual number of total and joint bleeds was significantly reduced from 35.8 to 4.1 and from 32.4 to 3.3 ($P < 0.01$). Again, these results were consistent with the outcomes reported in our series, with a reduction in total bleeds from 20.8 to 2.3 ($P < 0.0001$).

Validity of pharmacokinetics as a tool to individualize prophylaxis is supported by the results of a randomized comparison between a standard and a pharmacokinetic-tailored regimen prophylaxis in patients with haemophilia A. Valentino *et al.* [19] studied 66 patients between 7 and 56 years old, randomized to either a standard prophylactic regimen (20–40 IU/kg every other day) or a pharmacokinetic-tailored regimen (20–80 IU/kg every third day), with a target FVIII trough level of at least 1%. There was no statistical difference in annual bleeding rates between the two regimens (1.0 and 2.0 for standard and pharmacokinetic-tailored prophylaxis, respectively), consumption and adherence. Pharmacokinetic parameters of our series are quite similar to that of the study by Valentino *et al.*, with only a slightly lower CI (3.0 ± 1.0 vs. 3.89 ml/kg per h). That fact may reflect the older age of our population.

There is no evidence published to compare our tertiary prophylaxis consumption because most published data comes from secondary prophylaxis. There is only one study in which secondary prophylaxis and tertiary prophylaxis are described as one group [8,19]. The annual factor consumption under prophylaxis was 4552.0 IU/kg per year in the study by Collins *et al.* [8] and 3298.2 IU/kg per year in the study by Valentino *et al.* [19]. These are higher consumptions compared to our data (2374.2 IU/kg per year). This fact could be explained by the lower CI of our series because the patients were older.

Target trough FVIII level adjustment prophylaxis is able to improve results. Collins *et al.* stated that in patients aged between 10 and 65 years with severe haemophilia A, the annual number of bleeds during prophylaxis was 3.3, with a median time of plasma FVIII levels below 1 IU/dl of 16.5 h. The annual bleeding rate increased 1.4% for every hour that these levels persist [14]. Target trough FVIII levels are able to improve prophylaxis FVIII consumption. This observation is supported by Aznar *et al.* [13]. This is a prospective study of 15 adults (aged 26–47 years), who switch from on-demand to secondary prophylaxis. Doses and frequency of standard prophylaxis (35 IU/kg twice a week) were adjusted to trough FVIII levels between 1.5 and 2% in absence of spontaneous bleeding. Using this approach, they reduced total bleeding episodes (21.4 to 1.8; $P < 0.001$) and haemophilic arthropathy (12.6 to 1.4; $P < 0.001$) – thanks to prophylaxis schemes. After the adjustment of prophylaxis with trough FVIII levels, the consumption of FVIII was reduced by 21%. In our series, the introduction of trough FVIII level adjustments reduced FVIII consumption by 31.3% without changes in efficacy.

Life-long prophylactic factor replacement therapy is undoubtedly a costly intervention for health systems. This approach could be cost-effective when long-term benefits are considered (bleeding events avoided, osteo-muscular status improvement, fewer adverse effects and reduced hospitalizations) [20]. However, prophylaxis for patients with frequent haemorrhagic episodes is likely more cost-effective than for patients with few haemorrhagic episodes. The increase in factor consumption during prophylaxis compared with on-demand periods among adults under tertiary prophylaxis in our series was 50.7% and was comparable with that observed elsewhere [21]. The increase in consumption was lower in patients under tertiary prophylaxis to prevent haemophilic arthropathy (24.5%) than in patients who started for other reasons (73.9%), such as to prevent vital haemorrhage or to cover anti-platelet or anticoagulant treatment. Our results may also suggest that older patients with vascular comorbidities represent a particularly challenging group of patients to manage cost effectively, and that individualizing prophylaxis will be crucial.

Our study is one of the first examining adherence to prophylaxis only in adults. Ho *et al.* [22] have recently

published an adherence to frequency of 76% in a series of 31 adult patients on long-term prophylaxis with a method similar to the one we have used. Their results were close to the 84% we have described and to the data published by Tagliaferri *et al.* [18] and Valentino *et al.* [19], although their series includes adolescents and adults. This adherence is considerably higher than the 50% reported for other chronic diseases [23].

In addition, this is one of the first studies in which effectiveness of long-term tertiary prophylaxis due to vital haemorrhage, anti-platelet or anticoagulant treatment is described and analysed from FVIII consumption and cost point of view. In our study, all patients were managed at a single centre with the same protocols to treat and manage patients. This fact ensures the homogeneity of the data analysed.

There are some limitations to this study. Firstly, in this study, there is a lack of information about the evolution of physical performance and the quality of life in patients on long-term prophylaxis. Another limitation of the current study is the retrospective nature of the on-demand data and the short series. However, prophylaxis data are prospective and most of these patients are on tertiary prophylaxis. There is little published information on the optimal indication and management in this group. Moreover, this series is the second one reporting the benefits of pharmacokinetic-tailored and trough level prophylactic FVIII replacement therapy in the setting of tertiary prophylaxis. Taken together, the results reported here and those of Valentino *et al.*'s [19] study provide support for the validity of a pharmacokinetic-tailored trough FVIII level approach and the use of bleeding event rates to guide prophylaxis in adults with severe haemophilia A.

Conclusion

The observations reported provide further support for the efficacy of long-term prophylaxis in adult haemophilia A patients. In patients under primary and secondary prophylaxis, to carry on with these treatment schemes, not stopping due to adulthood, could be the key to maintaining an optimal joint status.

The use of an individualized approach to prophylactic FVIII replacement therapy using a pharmacokinetic-tailored and trough FVIII level approach could be a tool to optimize treatment. We have also shown that even patients with established arthropathy can achieve a significant reduction in bleeding events under a prophylactic regimen. Adherence in our cohort of patients was higher than that observed in the treatment of other chronic diseases and close to that of children and young adults.

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Conflicts of interest

The authors were solely responsible for the editorial content and approval of the submitted version.

The authors had no interests that might be perceived as posing a conflict or bias.

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