Choice of factor VIII/IX regimen in adolescents and young adults with severe or moderately severe haemophilia. A French national observational study (ORTHem 15-25)

Sandrine Meunier, Roselyne d'Oiron, H. Chambost, E. Dolimier, Benoît Guillet

Thrombosis Research 151 (2017) 17–22

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Choice of factor VIII/IX regimen in adolescents and young adults with severe or moderately severe haemophilia. A French national observational study (ORTHem 15-25)

Sandrine Meunier [a,*], Roseline d'oiron [b], Hervé Chambost [c], Edita Dolimier [d], Benoît Guillet [e], For the ORTHem 15-25 Study Group

Annie Borel-Derlon [f], Jeanne-Yvonne Borg [g], Hervé Chambost [h], Ségolène Claeyssens [i], Roseline d'Oiron [j], Valérie Gay [k], Stéphane Girault [l], Jenny Goudemand [m], Yves Gruel [n], Benoit Guillet [o], Abel Hassoun [p], Sandrine Meunier [q], Philippe Nguyen [r], Brigitte Pautard [s], Jocelyne Peynet [t], Chantal Rothschild [u], Jean-François Schved [v], Marc Trossaert [w], Alain Marques-Verdier [x]

[f] Centre Régional de Traitement de l'Hémophilie (CRTH) – CHU Caen, Caen, France
[g] Centre Hospitalier Régional Universitaire (CHRU), Hôpital Charles Nicolle, Rouen, France
[h] Centre de Traitement de l'Hémophilie, Hôpital La Timone, AP-HM and Inserm UMR S 1062, Aix Marseille University, Marseille, France
[i] CHRU Purpan – CRTH, Toulouse, France
[j] Hôpital de Bicêtre – Centre de Traitement de l'Hémophilie, Assistance Publique – Hôpitaux de Paris, Le Kremlin-Bicêtre, France
[k] Centre Hospitalier Général de Chambéry – Centre de Traitement de l'Hémophilie, Chambéry, France
[l] CHU de Limoges, Limoges, France
[m] Hôpital Cardiologique, CHRU Lille, Lille, France
[n] CHU Hôpital Trousseau – CRTH, Tours, France
[o] Hôpital Pontchaillou, CHU de Rennes, France and Inserm IRSET U1085, Rennes University 1, Rennes, France
[p] Groupe Hospitalier Simone Veil, Montmorency, France
[q] CRTH Lyon – Groupement Hospitalier, Bron, France
[r] CRTH, Hôpital Robert Debré, Reims, France
[s] CHRU Hôpital Nord, Amiens, France
[t] Centre Hospitalier de Versailles, Le Chesnay, France
[u] Groupe Hospitalier Necker-Enfant-Malade, Assistance Publique – Hôpitaux de Paris, Paris, France
[v] CHU de Montpellier – Hôpital Saint Eloi, Montpellier, France
[w] CHU de Nantes – Hôtel Dieu, Nantes, France
[x] Centre Hospitalier Universitaire (CHU) d'Estaing – CRTH Auvergne, Clermont-Ferrand, France:

[a] Haemophilia Treatment Centre, Louis Pradel Hospital, Bron, France
[b] Centre for Haemophilia and Rare Congenital Bleeding Disorders, AP-HP University Hospitals Paris-Sud, Bicêtre Hospital, Le Kremlin-Bicêtre, France
[c] Haemophilia Treatment Centre, AP-HM La Timone Hospital and Inserm UMR S 1062, Aix Marseille University, Marseille, France
[d] Baxalta France S.A.S., now part of Shire, Puteaux, France
[e] Haemophilia Treatment Centre, Pontchaillou Hospital, CHU Rennes and Inserm IRSET U1085, Rennes University 1, Rennes, France

ARTICLE INFO

Article history:
Received 24 October 2016
Received in revised form 19 December 2016
Accepted 23 December 2016
Available online 28 December 2016

Keywords:
Factor VIII
Factor IX
Prophylaxis
On-demand treatment

ABSTRACT

Introduction: The value and challenges of long-term prophylaxis (LTP) in adolescents and young adults need further characterisation.
Aim: To determine the proportions of adolescents and young adults with severe or moderately severe haemophilia in France under LTP and treatment on demand (OD).
Methods: Patients 15 to 25 years old with haemophilia A or B, factor VIII/IX ≤2% and no current inhibitor could be included if they had been under factor VIII/IX treatment at least 12 months and kept a treatment and bleeding diary.
Results: LTP was administered to 169/212 patients (79.7%) and OD treatment to 40/212 patients (18.9%). The most frequent reasons for initiating LTP were joint bleeding, target joints and frequent bleeds; whereas OD treatment was most often selected on the basis of mild bleeding phenotype or because of constraints on LTP. The mean annual bleed rate (ABR) in the OD group (6.33) was higher than in the LTP group (3.07, $p < 0.001$).

* Corresponding author at: Centre Régional de Traitement des Hémophiles, GHE – Hôpital cardiologique Louis Pradel, 59 Boulevard Pinel, 69677 Bron Cedex 03, France.
E-mail address: sandrine.meunier@chu-lyon.fr (S. Meunier).

http://dx.doi.org/10.1016/j.thromres.2016.12.023

Age groups
Haemorrhage

Mean ABR did not differ significantly between age strata (15–18, >18–21 and >21–25 years), but was significantly higher for patients with severe haemophilia (4.02) as compared to those with moderate haemophilia (1.97, $p = 0.002$). No significant difference was observed in mean ABR for joint bleeds between the LTP and OD groups. Physician reported LTP compliance was good or excellent in 97.0% of patients.
Conclusion: LTP is the predominant factor VIII/IX treatment among adolescents and young adults with severe or moderately severe haemophilia in France. LTP was associated with low ABR and high compliance.

1. Introduction

Prophylaxis has been shown to decrease chronic joint bleeds and chronic arthropathy in young children with haemophilia and has become standard-of-care treatment for patients with severe and moderately severe haemophilia in many countries [1–3]. Prophylactic treatment has been widely adopted in France since the 1990s, and in 2002 the French medical society, "Coordination Médicale pour l'Étude et le Traitement des maladies Hémorragiques constitutionnelles" (CoMETH), recommended long-term prophylaxis (LTP) in children with severe haemophilia A and B [4,5].

Most studies demonstrating the benefits of prophylaxis have involved young children. Less information is available on the use of prophylaxis in adolescents and young adults, an age span in which rapid growth is occurring and patients are assuming more decision-making and responsibility in their disease management [6]. Currently, there is no consensus on whether patients should remain on prophylaxis indefinitely as they make the transition into adulthood [3,7–9]. A recent study found that a switch from long-term prophylaxis (LTP) to treatment on demand (OD) in the late teens and early adulthood resulted in an increased number of bleeding events and a decreased quality of life [10].

Prophylaxis is burdensome, requiring regular infusions of replacement coagulation factor. A major concern in continuing prophylaxis has been that adolescents and young adults will be less adherent to the prescribed regimen [11–14]. Treatment patterns may be influenced by the health care system and the organisation of care for patients with haemophilia. No real-life data is available on the practice patterns for French adolescents and young adults with haemophilia A or B and factor VIII/IX ≤2% receiving a treatment regimen of either LTP or OD therapy.

The aim of our study was to document the practice patterns in this population.

2. Materials and methods

2.1. Design

This was an observational, multicentre, retrospective, real practice study conducted in haemophilia treatment centres (HTCs) in France to document practice patterns in adolescents and young adults with severe or moderately severe haemophilia A or B. All 40 French HTCs were invited to participate. The study was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL). Patients or, for those <18 years old, their parent/legal guardians were provided written information on the nature and objectives of the study and given the opportunity to decline participation. Patients were included between January 2010 and January 2012.

The primary objective was to determine the percentages of patients receiving LTP or OD treatment. Secondary objectives were to evaluate the history and characteristics of the patients, to determine the main reasons for initiating treatment and the duration of current treatment, to document regimen, factor usage, incidence of total and joint bleeds, target joint development, hospitalization due to bleeding events, and compliance with treatment.

2.2. Eligibility

Inclusion criteria consisted of: haemophilia A or B; age at inclusion from 15 to 25 years; factor VIII (FVIII) or IX (FIX) activity levels ≤2%; no current inhibitor; ≥12 months on LTP, OD treatment or other regimens not fulfilling the definitions of either LTP or OD; and a fully or partially completed haemophilia treatment diary covering a period of at least 3 years prior to inclusion. LTP was defined as at least 1 infusion of FVIII/FIX concentrate per week for a minimum of 46 weeks within a 52-week period and OD was defined as factor administration for the management of bleeding episodes only [15]. Patients were not eligible if they were participating in an interventional study or were on by-passing agent therapy during the study period.

2.3. Data collection

Data were collected from the patients' treatment and bleeding diaries and patients' medical records, from the last visit to the HTC retrospectively for at least one year and up to a maximum of 3 years. Data were recorded on standardized case report forms, which were completed by participating physicians, aided by a clinical trial technician if requested. They were entered into an anonymous database designed for the study.

Data collection encompassed extent of treatment diary completion; patient demographics; baseline FVIII/FIX activity level; type of haemophilia; F8/F9 genotyping if available; family history of haemophilia and viral infection; history of inhibitors and intracranial haemorrhage; age at first FVIII/FIX replacement treatment and first haemarthrosis; reasons for choice of replacement regimen; treatment duration, initiator and changes; type of FVIII/FIX concentrate administered; initial dosage and frequency of FVIII/FIX infusions; incidence of total bleeds; incidence and sites of joint bleeds; target joint development; compliance; and serious adverse events. The determination of annual bleeding rates (ABRs) was based on the information gathered from the treatment and bleedings monitoring diaries. Details on the circumstances and causes of bleedings were not collected. Target joints were defined as joints in which more than three bleeding episodes occurred over a 6-month period. No data on trough factor levels was collected. Compliance during prophylaxis was estimated by comparing the prescribed dosage written in the medical file and the frequency of FVIII/FIX infusions with the actual consumption as recorded in the treatment and bleedings diary. It was scored as excellent (75–100%), good (50 to <75%) or poor (25 to <50%) by the physician. In accordance with the Code de la Santé Publique, physicians involved in the treatment of the study patients were required to report promptly to the regional pharmacovigilance centre any serious or unexpected adverse event that may be due to a drug.

2.4. Statistical analysis

Descriptive statistics of data include mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum values for continuous data, absolute and relative frequencies for categorical data. Between-group differences were calculated by Fisher exact test

frequency for categorical data and non-parametric Krushkal Wallis test for continuous data. Total ABRs by group and severity and their 95% confidence interval (CI) were computed using contrasts with a negative binomial regression model to take into account the skewed distribution. The initial model included treatment group, age in category (15–18, >18 to 21) and severity as explicative variables. As the effect of age was not statistically significant (Khi^2 test), it was removed from the final model. Joint bleeds were computed by contrasts with negative binomial regression model with treatment group as explicative variable. Data were analysed using SAS® version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Centres

Of the 40 French CTHs that were invited to take part in the study, 19 actually included patients.

3.2. Patients

Two hundred and eighty-three patients were screened for eligibility (283), 69 were excluded, mostly because of missing treatment and bleedings diary (Fig. 1). The median number of included patients per centre was 7 (range, 2–42) for a total of 214 included patients. Two included patients did not satisfy all study eligibility criteria and were excluded from the analyses (Fig. 1). Of the 212 patients included in the analysis set, 169 were on LTP treatment, 40 on OD treatment and three on other regimens. One of these patients alternated between prophylaxis and OD treatment, another received preventive infusions before sports. In the third case, the other regimen included prophylaxis but was otherwise unspecified.

Among the 209 LTP and OD patients, the treatment and bleedings diary was fully completed by 173 of them (82.8%) and partly by 28 of them (13.4%). For the remaining 8 patients (3.8%), the level of completion of the treatment and bleeding monitoring diary was not specified. The mean (SD) age of first prophylactic treatment was 5.6 (2.9) years for patients 15–18 years old at inclusion, 7.2 (3.5) years in the >18 to 21 years age-range and 10.0 (5.0) years for those >21 to 25 years of age.

The baseline characteristics of the patients are summarised in Table 1. In the LTP group, the 15–18, >18 to 21, and >21 to 25 years age ranges were represented in similar proportions; whereas the preponderant age range of the OD group was >21 to 25 years, accounting for 60% of the total. The FVIII/FIX activity level was <1% in the majority of both the LTP and OD groups. Less than 10% of the LTP group was composed of patients with haemophilia B, compared with 25% of the OD group. The distribution of F8/F9 mutation types was consistent with that previously reported [16].

Patients of the LTP group had been under that regimen for a median of 10.9 years vs. 8.8 years for the OD group (Table 2). The LTP group had

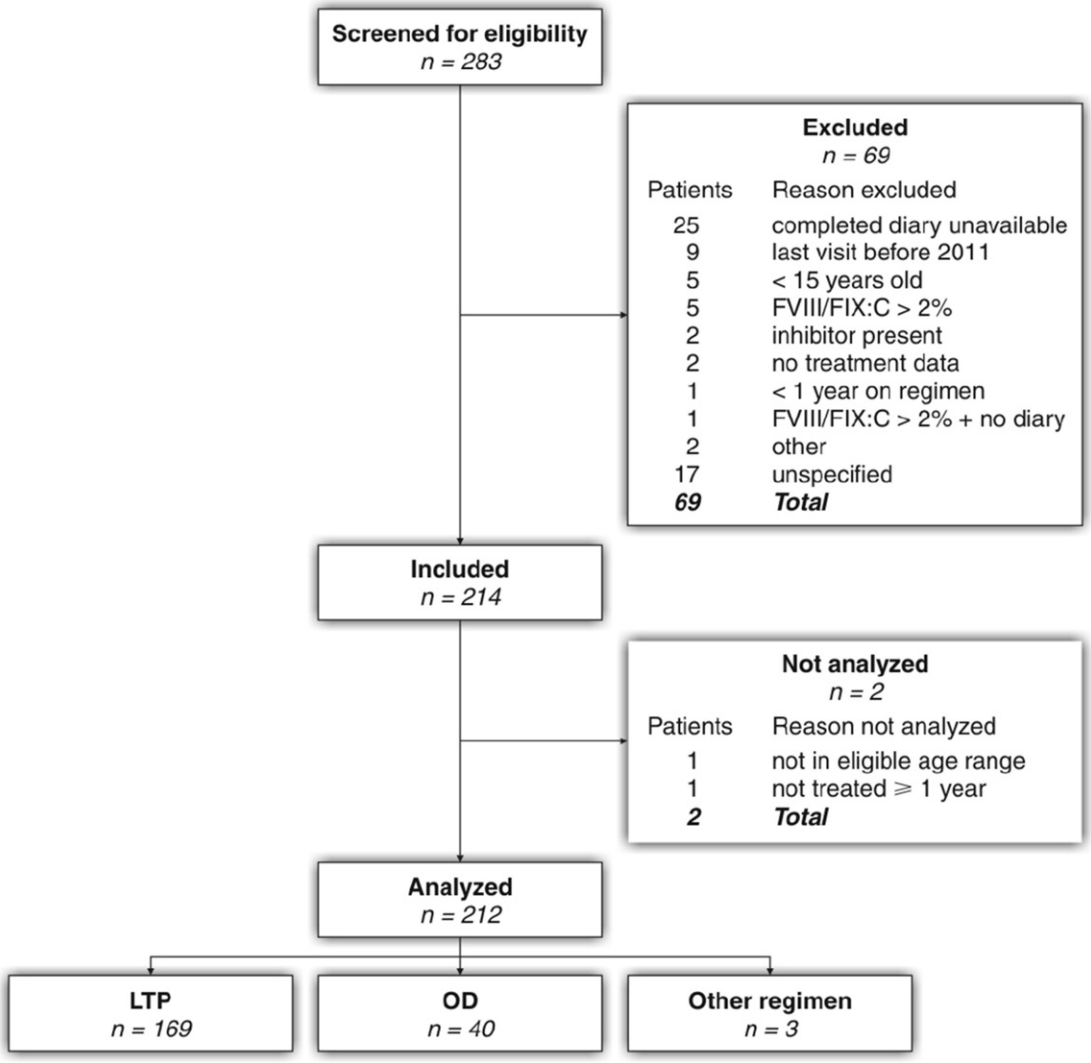

Fig. 1. Patient disposition.

Table 1
Patient's characteristics.

Characteristic n (%)	LTP (n = 169)	OD (n = 40)
Age (years)		
15–18	66 (39.1)	7 (17.5)
>18 to 21	49 (29.0)	9 (22.5)
>21 to 25	54 (32.0)	24 (60.0)
FVIII/FIX level (%)		
<1	145 (85.8)	26 (65.0)
1–2	24 (14.2)	14 (35.0)
Haemophilia type		
A	153 (90.5)	30 (75.0)
B	16 (9.5)	10 (25.0)
Known family history of haemophilia	68 (40.2)	21 (52.5)
Known family history of viral infection	4 (2.4)	3 (7.9)
History of inhibitors	36 (21.8)[a]	4 (10.0)
History of ICH	19 (11.3)[b]	3 (7.5)
Mutation[c]		
Intron 22 inversion	48 (30.8)	10 (28.6)
Other null	64 (41.0)	8 (22.9)
Non-null	44 (28.2)	17 (48.6)

Abbreviations: FIX, factor IX; FVIII, factor VIII; ICH, intracranial haemorrhage; LTP, long-term prophylaxis; OD, on demand.
[a] Data for 1 patient missing.
[b] Data for 4 patients missing.
[c] Data for 13 LTP and 5 OD patients missing.

started FVIII/FIX treatment at an earlier (p = 0.020) median age (1.1 years) than the OD group (1.3 years). They also experienced their first haemarthrosis at an earlier (p = 0.002) median age (2.7 years) than their OD counterparts (4.2 years).

3.3. Treatment

Diverse reasons prompted FVIII/FIX treatment, and more than a single reason could have been applicable in individual patients (Fig. 2). The most frequent reasons for initiating LTP were joint bleeding (50.9%), the presence of target joints (42.0%) and the occurrence of frequent bleeds

Table 2
Factor VIII/IX treatment.

Parameter	LTP (n = 169)	OD (n = 40)
Type of concentrate n (%)[a]		
Recombinant	160 (96.4)	34 (87.2)
Plasma-derived	6 (3.6)	5 (12.8)
Regimen duration (years); median (IQR)[b]	10.9 (8.2–13.8)	8.8 (4.1–19.4)
Age of first prophylactic treatment (years) median (IQR)	6.3 (4.5–9.5)	10.3 (7.0–12.3)
Age of treatment onset (years) median (IQR)	1.1 (0.7–1.6)	1.3 (1.0–3.0)
Age of first haemarthrosis (years) median (IQR)	2.7 (1.7–4.0)	4.2 (2.5–5.8)
Regimen initiator; n (%)[c]		
Physician	162 (97.6)	27 (73.0)
Patient	0 (0.0)	9 (24.3)
Parents	4 (2.4)	0 (0.0)
Physician + parents	0 (0.0)	1 (2.7)
Regimen changes over 3 years; n (%)		
0	75 (44.4)	4 (10.0)
1	46 (27.2)	3 (7.5)
2	23 (13.6)	33 (82.5)
3–5	25 (14.8)	0 (0.0)
Initial dose ($IU \cdot kg^{-1}$); mean (SD)	34.2 (8.1)[d]	–
Initial weekly infusions; median (range)	3 (1–7)[e]	–

Abbreviations: IQR, interquartile range; LTP, long-term prophylaxis; OD, on demand; SD, standard deviation.
[a] At enrolment; data for 3 LTP patients and 1 OD patient missing.
[b] For current Regimen; data for 8 LTP and 3 OD patients missing.
[c] Data for 3 LTP patients and 1 OD patient missing.
[d] Data for 2 patients missing.
[e] Data for 1 patient missing.

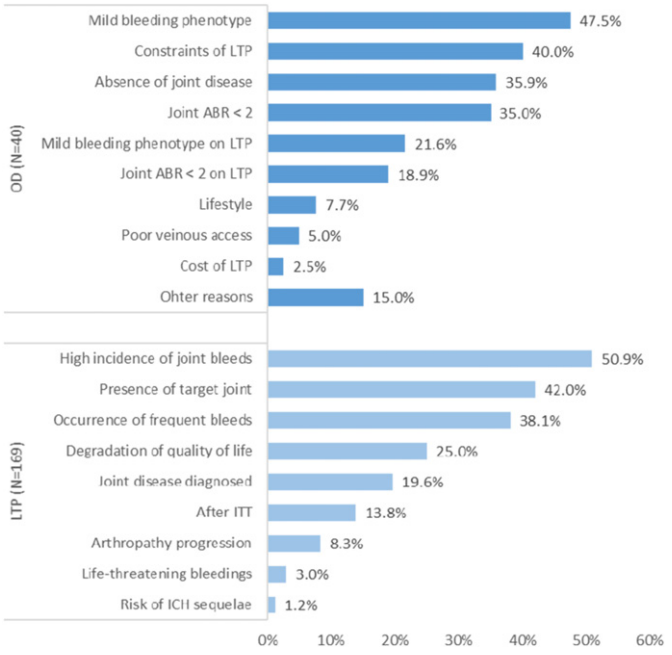

Fig. 2. Reasons for initiating LTP or OD treatment. Abbreviations: ABR, annual bleeding rate; ICH, intracranial haemorrhage; ITT, Immune tolerance treatment; LTP, long-term prophylaxis; OD, on demand.

(38.1%). Most of the common reasons for selecting OD treatment concerned the absence of frequent or serious bleeding and associated morbidity: mild bleeding phenotype (47.5%), no arthropathy (35.9%), fewer than 2 joint bleeds per year (35.0%), and mild (21.6%) or infrequent (18.9%) bleeding on LTP. The other common basis for OD treatment was constraints on LTP (40.0%).

The included patients preponderantly received recombinant FVIII/FIX concentrates (Table 2). The physician was the most common regimen initiator in both groups. Over the 3-year study period the LTP regimen was seldom changed: either no change or only a single change was instituted in 71.6% of that group. By contrast, the OD regimen was changed twice in 82.5% of patients.

The initial dose for LTP averaged 34.2 $IU \cdot kg^{-1}$ (Table 2). A median of 3 prophylactic infusions per week were administered initially in the LTP group. Of the 169 patients on LTP, compliance was rated by the physicians as excellent in 146 (86.4%), good in 18 (10.7%) and poor in 5 (3.0%).

3.4. Bleeding

During the 3-year study period, 140 patients of the LTP group (82.8%) and 39 of the OD group (97%) experienced at least one bleeding episode (p = 0.021). Bleeding episodes were significantly more frequent in the OD (6.33) than the LTP group (3.07, p = 0.0005). The ABR did not differ significantly between age classes (data not shown, p = 0.76), but was significantly higher in patients with severe haemophilia (4.02) than in patients with moderate haemophilia (1.97, p = 0.002) (Fig. 3). Over the 12-month period prior to study inclusion, seven patients of the LTP group (4.1%) and three of the OD group (7.5%) were hospitalized for bleeding.

Joint bleeds were more frequent in the OD group (1.20) than in the LPT group (0.79); however, the difference was not statistically significant (p = 0.15, Table 3). Joint bleeds were more frequent in patients with severe haemophilia (0.98) than in patients with moderate haemophilia (0.49, p = 0.04). The sites most often affected in both groups were the ankle, elbow and knee (Table 3).

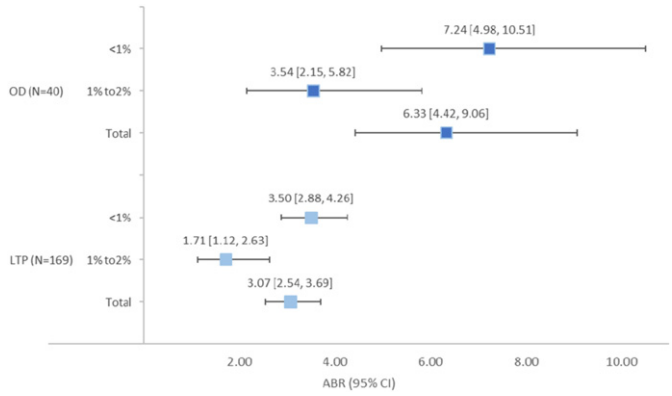

Fig. 3. ABR in the LTP and OD groups in patients with severe or moderately severe haemophilia. Contrast model adjusted ABR and 95% CI were computed by negative binomial regression with treatment group and severity as explicative variables. Error bars indicate 95% CI. Abbreviations: ABR, annual bleed rate; CI, confidence interval; LTP, long-term prophylaxis; OD, on demand.

3.5. Target joints

Twelve LTP patients (7.1%) developed new target joints over the course of the 3-year study period. Such target joints arose in 5 patients of the OD group (12.5%).

3.6. Safety

No serious adverse event was observed.

4. Discussion

In this study conducted in French HTCs, almost 80% of 212 patients with severe haemophilia (FVIII/FIX < 2%) aged 15–25 years had received LTP for a median of 11 years. LTP patients displayed low annual rates of total bleeds, infrequent haemarthroses and high compliance to therapy.

The cohorts in this study, who were born between 1985 and 1996, stand at the leading edge of French haemophilia patients on LTP. During the time of their birth and early childhood, LTP was just becoming widely available in France [17]. The median age at which the LTP patients began prophylaxis was 6.3 years, and thus their regimen can be essentially classified as secondary prophylaxis. The average age at which prophylaxis is begun in French children has continued to decline. By the period 2004–2007, prophylaxis was begun at 1.8 and 1.4 years in severe haemophilia A and B patients, respectively, marking a shift toward primary prophylaxis [5].

Most of the patients in the study had haemophilia A, and of those 84% were under LTP; whereas, 62% of the haemophilia B patients were receiving LTP. Several other studies provide data on the percentages of adolescents and young adults receiving LTP or OD treatment [18,19]. In one of those reports, a 2010 practice patterns survey in the US, 73% patients aged 13–24 years of age with severe haemophilia A were on primary or secondary prophylaxis [20], compared with the 84% in the present study. In patients with severe haemophilia B, 64% were receiving prophylaxis, compared with 62% of our patients.

Prophylactic regimens in our population were generally stable, with no change or only one change being made during the preceding 3-year period in almost three-quarters of patients. The bleeding rate was low, with a mean ABR for total bleeds of 3.07and joint bleeds of 0.60. Knee joint bleeds were infrequent. These rates are in close agreement with those reported in a number of other studies involving LTP in adolescents and/or young adults [6,8,10,21].

A major concern regarding the continuation of LTP in adolescents and young adults is potentially reduced adherence to therapy [9,11–13,22]. Patients usually assume responsibility for their own care during adolescence. In a Scandinavian study patients took responsibility at a mean age of 14.1 years [12].

According to a recent study, better adherence to the prescribed treatment regimen was accompanied by less chronic pain among adolescents and young adults with moderate or severe haemophilia [23]. Social pressures and lifestyle changes may cause high compliance with prophylactic treatment to become a lower priority for patients during this phase of life. In a recent survey of US haemophilia healthcare professionals, only an estimated 20% of patients aged 13 to 18 years administered ≥80% of prescribed prophylaxis [13]. By contrast, in the current study compliance with therapy was rated as excellent in 86% of patients, good in 11% and poor in only 3%. An eligibility criterion of our study was a fully or partially completed haemophilia treatment diary covering a period of at least 3 years prior to inclusion, and this requirement could have selected for patients who are particularly diligent. Nevertheless, of the 283 patients screened for study eligibility only 9% were excluded due to lack of a completed diary. A maximum bias hypothesis considering that all excluded patients were on LTP and adhered poorly to the treatment, leads to an excellent adherence to treatment rate of 61%. So it appears unlikely that the high rate of adherence to therapy can be ascribed to selection bias.

The goal of this study was to characterize the type of treatment regimens utilized in patients spanning the age range of 15 to 25 years. Among the 20% of study patients receiving OD treatment, the most frequent reasons for the choice of this regimen were related to mild bleeding phenotype. Selection of such patients is reflected in the relatively low ABR of 6.33 for total bleeds. While this ABR was more than twice as high as that of patients on LTP (Fig. 3), it was nonetheless low compared to expected bleed rates in the general population of haemophilia patients receiving OD treatment. In a recent retrospective multicentre US study of older adolescents and young adults, the ABR for total bleeds was 24 among patients receiving OD treatment [10]. In an Italian study, adolescents receiving OD treatment averaged 34 total bleeds annually [6]. Total joint bleeds in our study were also low (ABR 1.16) for the OD treatment group. Therefore, these patients appear to constitute a subset with a milder bleeding pattern that can be managed satisfactorily without recourse to prophylaxis.

This retrospective study was not specifically designed to assess safety. While no serious adverse drug-related events were reported, surveillance was passive, and hence some such adverse events could potentially have eluded observation.

A 2007 practice pattern survey of 21 European haemophilia physicians posed the question of whether prophylaxis should be used in adolescent and adult patients [9]. The survey revealed that the majority of physicians would consider modifying established prophylaxis in the adolescent age group, and the preferred age for modification was 16–20 years old. The physicians indicated that approximately half of a cohort of 218 patients with severe haemophilia successfully reduced or stopped prophylaxis when they reached adolescence. The current study suggests that during adolescence and young adulthood patients were still benefitting from and adhering to prophylaxis. How long prophylaxis should be continued and at what intensity remains unresolved.

Table 3
Joint bleeds.

Joint ABR (95% CI)	LTP (n = 169)	OD (n = 40)
Total	0.79 (0.62–1.02)	1.20 (0.73–2.00)
Ankle	0.42 (0.31–0.57)	0.38 (0.19–0.75)
Elbow	0.22 (0.16–0.33)	0.48 (0.27–0.85)
Knee	0.14 (0.09–0.21)	0.19 (0.09–0.41)
Shoulder	0.04 (0.02–0.08)	0.10 (0.03–0.28)
Hip	NE	NE

Contrast model adjusted ABR and 95% CI were computed by negative binomial regression with treatment group as explicative variables.
Abbreviations: ABR, annual bleed rate; CI, confidence interval; LTP, long-term prophylaxis; NE, not evaluable; OD, on demand.

Arguments have been made that prophylaxis should be lifelong [24]. As more and more patients who have started prophylaxis at an early age reach adolescence, questions regarding the optimal use of prophylaxis and how best to identify individuals who will continue to benefit from this regimen will become more pressing.

5. Conclusion

In France, approximately 80% of adolescents and young adults with severe haemophilia receive prophylactic treatment with factor VIII/IX concentrates. These patients are generally highly compliant to their treatment, and their bleeding rate is correspondingly low. The low ABR in patients receiving OD treatment suggests that the choice of treatment regimens is based primarily on bleeding patterns in this age group.

Acknowledgement

The ORTHem 15-25 study was sponsored by Baxalta France S.A.S., now part of Shire.

The authors contributed to the concept and design of the study. They also contributed to the review and edits of the manuscript. The authors recognize and thank the investigators from the ORTHem 15-25 Study Group, for successfully conducting the study.

Finally, we would like to thank Dr. Béatrice Villette, former Medical Director at company, who contributed in substantive way to the project.

References

[1] M.J. Manco-Johnson, T.C. Abshire, A.D. Shapiro, B. Riske, M.R. Hacker, R. Kilcoyne, et al., Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia, N. Engl. J. Med. 357 (2007) 535–544.
[2] A. Gringeri, B. Lundin, S. von Mackensen, L. Mantovani, P.M. Mannucci, A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT study), J. Thromb. Haemost. 9 (2011) 700–710.
[3] A. Srivastava, A.K. Brewer, E.P. Mauser-Bunschoten, N.S. Key, S. Kitchen, A. Llinas, et al., Guidelines for the management of hemophilia, Haemophilia 19 (2013) e1–47.
[4] S. Meunier, M. Trossaert, C. Berger, A. Borel-Derlon, G. Dirat, S. Donadel-Claeyssens, et al., Prophylaxie de longue durée chez les enfants hémophiles A et B sévères en prévention de l'arthropathie hémophilique, Arch. Pediatr. 16 (2009) 1571–1578.
[5] S. Meunier, H. Chambost, V. Demiguel, A. Doncarli, F. Suzan, M. Trossaërt, Use of clinical practice guidelines on long-term prophylaxis in severe hemophilia in France: a retrospective audit, J. Pediatr. 162 (2013) 1241–1244 4 e1.
[6] A. Tagliaferri, M. Franchini, A. Coppola, G.F. Rivolta, C. Santoro, G. Rossetti, et al., Effects of secondary prophylaxis started in adolescent and adult haemophiliacs, Haemophilia 14 (2008) 94551.
[7] K. Fischer, J.G. Van Der Bom, R. Prejs, E.P. Mauser-Bunschoten, G. Roosendaal, D.E. Grobbee, H.M. Van Den Berg, Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome, Haemophilia 7 (2001) 544–550.
[8] K. van Dijk, K. Fischer, J.G. van der Bom, E. Scheibel, J. Ingerslev, H.M. van den Berg, Can long-term prophylaxis for severe haemophilia be stopped in adulthood? Results from Denmark and the Netherlands, Br. J. Haematol. 130 (2005) 107–112.
[9] M. Richards, C. Altisent, A. Batorova, H. Chambost, G. Dolan, P. de Moerloose, et al., Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data, Haemophilia 13 (2007) 473–479.
[10] M.J. Manco-Johnson, J. Sanders, N. Ewing, N. Rodriguez, M. Tarantino, T. Humphries, Consequences of switching from prophylactic treatment to on-demand treatment in late teens and early adults with severe haemophilia A: the TEEN/TWEN study, Haemophilia 19 (2013) 727–735.
[11] K. Fischer, L. Valentino, R. Ljung, V. Blanchette, Prophylaxis for severe haemophilia: clinical challenges in the absence as well as in the presence of inhibitors, Haemophilia 14 (Suppl. 3) (2008) 196–201.
[12] K. Lindvall, L. Colstrup, I.M. Wollter, G. Klemenz, K. Loogna, S. Gronhaug, H. Thykjaer, Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia, Haemophilia 12 (2006) 47–51.
[13] C.D. Thornburg, S. Carpenter, S. Zappa, J. Munn, C. Leissinger, Current prescription of prophylactic factor infusions and perceived adherence for children and adolescents with haemophilia: a survey of haemophilia healthcare professionals in the United States, Haemophilia 18 (2012) 568.
[14] P. Petrini, A. Seuser, Haemophilia care in adolescent – compliance and lifestyle issues, Haemophilia 15 (Suppl. 1) (2009) 15–19.
[15] S. Donadel-Claeyssens, on behalf of the European Paediatric Network for Haemophilia Management, Current coordinated activities of the PEDNET (European Paediatric Network for Haemophilia Management), Haemophilia 12 (2) (2006) 124–127.
[16] C.H. Miller, J. Benson, D. Ellingsen, J. Driggers, A. Payne, F.M. Kelly, et al., F8 and F9 mutations in US haemophilia patients: correlation with history of inhibitor and race/ethnicity, Haemophilia 18 (2012) 375–382.
[17] H. Chambost, R. Ljung, Changing pattern of care of boys with haemophilia in western European centres, Haemophilia 11 (2005) 92–99.
[18] T.T. Biss, A.K. Chan, V.S. Blanchette, L.N. Iwenofu, M. McLimont, M.D. Carcao, The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey, Haemophilia 14 (2008) 923–930.
[19] D. Noone, B. O'Mahony, L. Prihodova, A survey of the outcome of prophylaxis, on-demand or combined treatment in 20–35 year old men with severe haemophilia in four European countries, Haemophilia 17 (2011) e842–e843.
[20] S. Zappa, M. McDaniel, J. Marandola, G. Allen, Treatment trends for haemophilia A and haemophilia B in the United States: results from the 2010 practice patterns survey, Haemophilia 18 (2012) e140–e153.
[21] J. Ingerslev, S. Lethagen, L. Hvitfeldt Poulsen, B. Sorensen, E. Lopatina, I. Tentsova, et al., Long-standing prophylactic therapy vs. episodic treatment in young people with severe haemophilia: a comparison of age-matched Danish and Russian patients, Haemophilia 20 (2014) 58–64.
[22] K. Khair, F. Gibson, L. Meerabeau, The benefits of prophylaxis: views of adolescents with severe haemophilia, Haemophilia 18 (2012) e286–e289.
[23] J.M. McLaughlin, M.L. Witkop, A. Lambing, T.L. Anderson, J. Munn, B. Tortella, Better adherence to prescribed treatment regimen is related to less chronic pain among adolescents and young adults with moderate or severe haemophilia, Haemophilia 20 (2014) 506–512.
[24] M. Makris, Prophylaxis in haemophilia should be life-long, Blood Transfus. 10 (2012) 165–168.