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Original article

Clinical outcome and incidence of inhibitor development in severe hemophilia patients receiving low-dose prophylaxis: a 3-year follow-up study in Senegal, West Africa

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ABSTRACT

Introduction: In Africa, where access to diagnosis and treatment of hemophilia is the lowest in the world, prophylaxis is rarely used in preference to on-demand treatment. There are limited data of prophylaxis treatment from sub-Saharan Africa. The aim of this study was to evaluate clinical outcomes and inhibitor development in people with hemophilia receiving low-dose prophylaxis (LDP) in a sub-Saharan African setting.

Methods: We conducted a three-year prospective study. A once or twice weekly prophylaxis regimen of 25 IU/kg of rFVIIIFc or 30 IU/kg of rFIXFc was given to Hemophilia A and B, respectively. We evaluated clinical outcomes and inhibitors occurrence, determined by screening and titration using the Nijmegen technique.

Results: A total of 15 patients were included in the LDP regimen. The mean age was 6.3 years (1.5 - 10). A significant reduction was noted in the annualized bleeding rate, from 7.53 to 1.33 ($p = 0.0001$); the annualized joint bleeding rate passed from 3.6 to 1.4 ($p = 0.001$) and the proportion of severe bleeding, from 86.1% to 16.7% ($p = 0.0001$). The Hemophilia Joint Health Score (HJHS) moved from 9.6 to 3.4 ($p = 0.0001$) and the Functional Independence Score in Hemophilia (FISH) improved from 25.8 to 30.9 ($p = 0.0001$). School absenteeism decreased from 7.33% to 2.59%. Adherence to prophylaxis was 89.5% *versus* 60%. Consumption was 580 IU/kg/year *versus* 1254.6 IU/kg/year before and after prophylaxis, respectively. Incidence of inhibitors was 23% (3 /13 HA).

Conclusion: The LDP in Hemophilia improves the clinical outcome without a surplus risk of inhibitor development. Using extended half-life clotting factor concentrates (CFCs) is better for prophylaxis in resource-limited countries, as they allow better compliance in treatment.

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Introduction

Prophylaxis therapy with clotting factor concentrates (CFCs) is the standard of care for patients with severe hemophilia.[1] Different protocols are used with different doses and injection frequencies, but an optimal regimen remains to be defined.[2,3]

Due to the limited availability of CFCs in Africa, prophylaxis is rarely used in favor of on-demand (OD) treatment.[4] However, emerging data suggest that low-dose prophylaxis (LDP) can be a viable option for improving joint health and physical independence.[5–8] Currently, there are very limited data from sub-Saharan Africa, where access to diagnosis and treatment is the lowest in the world.[9]

Apart from the efficacy of LDP, the risk of developing inhibitors is a concern for patients and health care professionals. The occurrence of inhibitors increases the risk of the following adverse outcomes: uncontrolled bleeding and disability due to joint destruction, reduced quality of life and an increased risk of death, as well as difficulty in managing the disease.[10] This is especially true in low-income countries, where the means of diagnosing and treating inhibitors are often lacking. Fear of inhibitor development may be a limitation to extending the LDP regimen in hemophilia care in Africa, despite some studies showing a protective effect of prophylaxis against the development of inhibitors.[11,12] The implementation of LDP in Africa was facilitated by the procurement of extended half-life CFCs as part of the World Federation of Hemophilia (WFH) humanitarian Aid Program,[13] which improves access to treatment, et allows better follow-up of patients.

The International Hemophilia Treatment Center (IHTC) of Dakar (Senegal) has been organizing a hemophilia cohort follow-up since 1995 and significant progress has been made; specifically, diagnosis of new patients, reduced mean age at diagnosis and a lower mortality rate,[14] as well as improved quality of data collection.[15] For 3 years, an LDP program was implemented along with a prospective follow-up, consisting of a clinical outcome assessment and systematic inhibitor screening. This study aimed to evaluate the clinical outcomes and incidence of inhibitor development in severe hemophilia patients receiving LDP in a sub-Saharan African setting.

Methods

Patients

Inclusion criteria in the LDP group were as follows: age under 10 years; regular follow-up at the IHTC, with at least one visit every three months; absence of inhibitors; absence of severe arthropathy; having had at least one joint bleeding, and; parental approval. Patients who had difficulty accessing the center regularly were not included, nor were those who had poor venous access.

Methods

A 3-year prospective study was conducted from February 2017 to March 2020. A once- or twice-weekly prophylaxis regimen of 25 IU/kg of FVIII or 30 IU/kg of FIX was administered to hemophilia A (HA) and hemophilia B (HB) patients, respectively, as defined in the protocol (Figure 1). All patients were treated with extended half-life recombinant Fc fusion rFVIII (Eloctate*) for HA and rFIX (Alprolix*) for HB. Patients' baseline data was collected from medical records available at the IHTC and all data since the beginning of prophylaxis were registered on a medical record chart that was used during

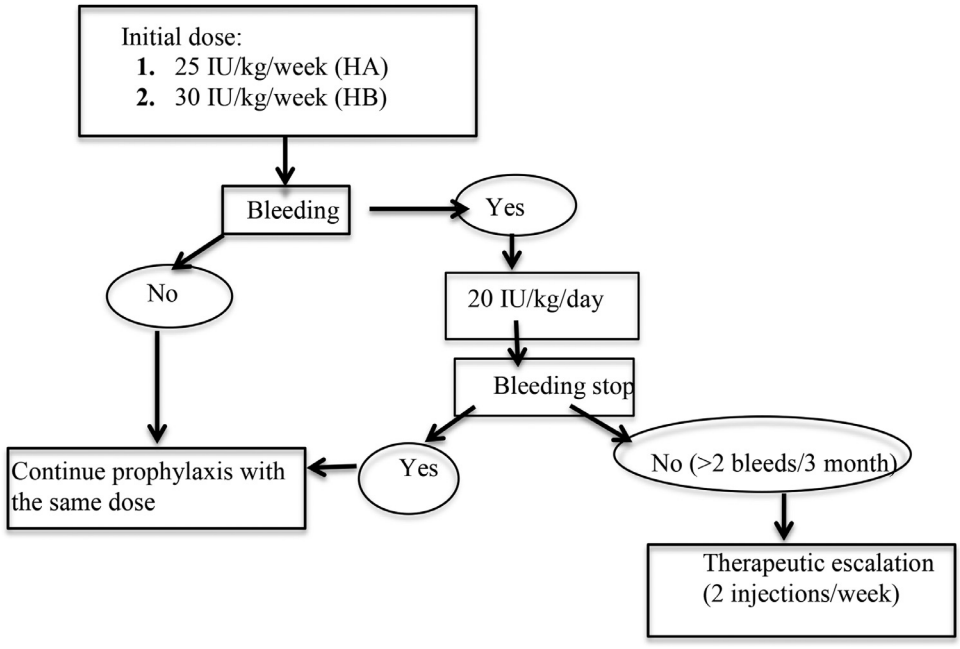

Figure 1 – Prophylaxis protocol. Note: HA: hemophilia A; HB: hemophilia B.

follow-up. Informed consent was obtained from the patients' parents or legal guardians for all participants.

Outcome measures included annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), and number of severe bleeds (*i.e.*, a life-threatening bleeding or joint bleeds / muscular bleeds not resolved after 24 hours, despite treatment). Joint health was assessed using the Hemophilia Joint Health Score (HJHS) version 2.2, and patient functional ability was assessed using the Functional Independence Score in Hemophilia (FISH).

A trained physician conducted the assessment of these two scores at the baseline and 3-year follow-up. We also assessed school absenteeism, defined as the total number of days of absence due to a bleeding episode over the total number of school days. Adherence to the prophylaxis regimen was assessed by calculating the treatment attendance rate: for patients on LDP, the number of doses taken out of the planned number of doses, and for those on OD treatment, the number of acute bleeding episodes treated with a CFC out of the number of acute bleeding episodes requiring treatment with a CFC.

Inhibitors were screened during regular intervals. Plasma samples were obtained from patients who were on LDP at T0 (before starting LDP), T1 (10 exposure days (EDs)), T2 (25 EDs) and T3 (50 EDs). The Nijmegen modification of the Bethesda assay was used to detect inhibitors. The presence of inhibitors was then evaluated in the different samples. Furthermore, risk factors associated with the development of inhibitors were studied as follows: family history of inhibitors; age at first exposure to CFCs; surgery; concomitant infectious episodes during CFC injections; CFC consumption before prophylaxis; number of different types of used CFCs before prophylaxis, and; adherence.

We compared patients in pre- and post-prophylaxis periods.

The study was approved by the local Ethics Committee. All data were registered in the SPSS 18 software (IBM, USA). The descriptive study was performed by calculating the mean (minimal and maximal values) and frequencies. Comparison of means and percentages was performed using the Student's t-test, Chi-square test and exact Fischer test, based on their applicability. Statistical significance was set at $p < 0.05$.

Results

Twenty-seven patients were pre-included but only 15 patients who met all the inclusion criteria were definitively included in this study on LDP.

The mean age was 6.3 (1.5 – 10). Nine of the 15 patients lived in Dakar, while six lived in other cities located 70 to 200 km away. Two patients (13.3%) were on primary prophylaxis (one previously untreated patient (PUP)), nine patients (60%), on secondary prophylaxis and four, on tertiary prophylaxis (26.7%). The initiation of prophylaxis was performed in patients aged 3 years or younger (n = 2), 4 to 6 years (n = 4) and 7 to 10 years (n = 9). One HA patient received an increase of two injections per week after 1 year of prophylaxis. Before entering the LDP regimen, 14 of the 15 patients had already received one to four different CFCs for acute bleeding treatment, with a mean of 10.93 (0 – 23) exposure days.

Table 1 – General characteristics of patients.

Variables	Number (n = 15)	%
Type of hemophilia:		
- A	13	86.7
- B	2	13.3
Age of initiation prophylaxis:		
- ≤ 3 years	2	13.3
- 4 – 6 years	4	26.7
-7 – 10 years	9	60
Type of prophylaxis:		
- Primary	2	13.3
- Secondary	9	60
- Tertiary	4	26.7
Type of patients:		
- PUPs	1	6.7
- PTPs	14	93.3
Different CFC used at inclusion (n):		
- 0	1	6.6
- 1	5	33.4
- 2	3	20
- 3	4	26.6
- 4	2	13.4
No. of EDs at inclusion	10.9 (0–23)	
Number of doses:		
- 1 dose /week	14	93.3
- Escalade (2 doses/week)	1 HA	6.7

PUPs: previously untreated patients; PTPs: previously treated patients; CFCs: clotting factor concentrates; EDs: exposure days.

At inclusion, the number of previous CFC EDs was 10.93 (0 – 23) (Table 1).

After comparing the clinical outcomes at the completion of a 3-year follow-up, we observed that the ABR was significantly decreased ($p = 0.0001$), from an average of 7.53 (median: 7 and SD: 3.5) to 1.33 (median: 1 and SD: 0.89); the AJBR passed from a mean of 3.6 (median: 3 and SD: 1.78) to 1.4 (median: 0 and SD: 0.54) ($p = 0.001$). Severe bleeding was significantly decreased, compared to its previous state (86.1% *vs.* 16.7%) ($p = 0.0001$). The HJHS decreased from a mean of 9.6 (median: 9 and SD: 4.85) to 3.4 (median: 1 and SD: 5.2) ($p = 0.0001$). The FISH score significantly improved from an average of 25.8 (median: 28 and SD: 3.66) to 30.9 (median: 31 and SD: 1.56) ($p = 0.0001$). It was equal to 32/32 in 10 patients and between 27 and 30 in five patients and was stable for all patients during prophylaxis (Figure 2).

The number of missed days owing to a bleeding episode over the total number of school days decreased from 7.33% to 2.59% ($p = 0.049$) and the compliance of treatment measured by the treatment attendance rate as the number of actual doses taken out of the planned number of doses was 89.5% after prophylaxis, compared to 60% before prophylaxis ($p = 0.05$). The CFC consumption was 580 IU/kg/year (SD: 429.014) before, and 1254.6 IU/kg/year (SD: 259.07) after, prophylaxis (0.001) (Table 2).

Three HA patients developed inhibitors, with a global incidence of 23% (3/13 HA), and all were low responders. The incidence of high-responding inhibitors was zero. These inhibitors occurred only among HA patients on T2 samples

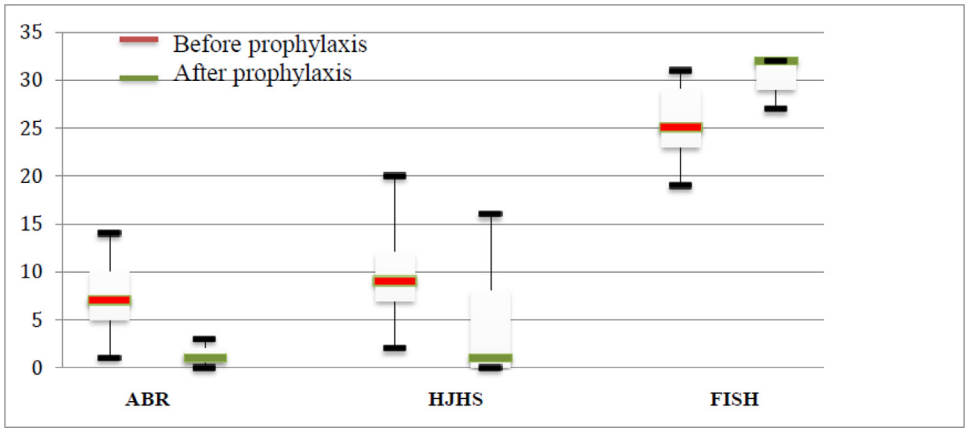

Figure 2 – Comparison of ABR, HJHS and FISH in patients on prophylaxis before and after a 3-year follow-up. Note: ABR: annual bleeding rate; HJHS: Hemophilia Joint Health Score; FISH: functional independence score in hemophilia.

(2 BU) and T3 samples (3 BU and 5 BU). The only PUP had developed a transient inhibitor in 25-ED samples (2 BU) that disappeared in 50 EDs. However, none of these inhibitors proved to be clinically relevant. The identified risk factors associated with inhibitor development were treatment of breakthrough bleeding (p = 0.009) and the existence of an infectious event during prophylaxis (p = 0.004).

We found a statistically significant association between inhibitor development and the following factors: age at first exposure 18.6 (2 – 60) months versus 25.1 (3 – 72); family history of inhibitor, one in each group; different types of priorly used CFCs, 4 (3 – 5) *versus* 2.64 (1 – 5); CFC consumption before prophylaxis, 7,053.7 IU/year versus 4,826.7 IU/y, and; treatment adherence rate, 93.9% *versus* 97.6%. One minor surgery (circumcision) was performed in inhibitor-positive patients (Table 3).

Discussion

Of the 27 patients pre-included at the beginning of the study, 12 did not benefit from the LDP program. Barriers that excluded them permanently from this program were living in a residence far away from the health service and the parental lack of motivation for regular follow-up, primarily due to the fear of additional out-of-pocket healthcare costs. Therefore, the availability of CFCs is not the only factor to consider; others include social support and an improvement of geographic and financial accessibility to care. This would enable the LDP to benefit more hemophilia patients, recommended by the World Health Organization as part of universal health coverage. In addition to developing home treatment, the use of emicizumab will likely encourage patient acceptance of prophylaxis by reducing the patient's dependence on a healthcare system that is not always accessible to them.

This study contains one of the longest follow-up periods (3 years) of hemophilia patients treated with LDP and provides real-world data from a sub-Saharan African setting. These results are consistent with those previously reported from Tunisia,[6] India,[7] China,[8] Iran[16] and Côte d'Ivoire,[17] in terms of a significant reduction in the ABR and the proportion of severe bleeds, compared to the OD treatment in particular. The benefits of LDP are more evident in the same patients before and after prophylaxis, in terms of the reduction in ABR, AJBR and severe bleeding and better HJHS and FISH scores. Furthermore, the number of missed days owing to a bleeding episode over the total number of school days decreased from 7.33% to 2.59%.

Table 2 – Clinical outcomes before and after prophylaxis.

Variables	Before prophylaxis (Mean/SD/Intervals)	After prophylaxis (Mean/SD/Intervals)	p-value
ABR	7.53/year; 3.5; [1 - 14]	1.33/year; 0.89; [0 - 3]	0.0001
AJBR	3.6/year; 1.78; [1 - 6]	1.4/year; 0.54; [0 - 3]	0.0001
Severity of bleeding			
Minor	13.9%	83.3%	0.0001
Severe	86.1%	16.7%	
HJHS	9.6; 4.85; [2 - 20]	3.4; 5.2; [0 - 16]	0.0001
FISH	25.8; 3.66; [19 - 31]	30.9; 1.56; [27 - 32]	0.0001
School absenteeism	7.33%	2.59%	0.049
Treatment attendance rate	60%	89.5%	0.05
Mean CFCs Consumption	580 IU/kg/year; 429.014 [0 - 1357]	1254.6/kg/year; 259.07 [1130 - 2116]	0.001

ABR: annualized bleeding rate; AJBR: annualized joint bleeding rate; HJHS: Hemophilia Joint Health Score; FISH: functional independence score in hemophilia.

Table 3 – Risk factors associated with inhibitors development.

Risk factors	Permanent inhibitor + n = 2	Inhibitor - n = 13	*p*-value
Age at first exposure (month)	18.6 (2 – 60)	25.1 (3 – 72)	0.945
Family history (n)	1 ➔ 2nd degree	1 ➔1rst degree	0.476
Switch CFCs (n)	2 (3 – 5)	2.64 (1 – 5)	0.072
Consumption before prophylaxis (IU)	7053.75	4826.7	0.495
Treatment of a breakthrough bleed (n)	2	1	0.009
Surgery (n)	1 (circumcision)	0	0.267
Occurrence of infections (n)	2	4	0.004
Level of adherence to treatment (n)	0	9	0.051

CFCs: clotting factor concentrates.

These results serve to motivate governments to maintain a supply of CFCs to support this type of treatment, as it significantly improves patient outcomes and does not rely solely on World Federation of Hemophilia (WFH) humanitarian donations. Although prophylaxis appears to be costly, it is more beneficial and cost-effective than treatment on demand, especially in the long term. It would allow better optimization and rationalization of CFC use.

It is well recognized that the earlier the prophylaxis is started, the better the HJHS becomes. This may explain the fact that, although more than half of our patients were on secondary or tertiary prophylaxis, they were all under 10 years old. The FISH score was better during prophylaxis. This result supports the goals of prophylaxis in achieving a better quality of life and active participation in daily life. Other studies have also failed to show any significant improvement or stable scores for HJHS and FISH.[18,19]

The protocol used in our study included only one injection per week, which does not allow optimal coverage after the third day for rFVIII. It appears more beneficial to maintain a frequency of at least two injections per week. A model-based evaluation of LDP in HA showed that using 10 IU/kg twice per week resulted in a median relative risk of annualized bleeds of 1.34, with an 83.3% cost reduction.[20]

One of the biggest challenges regarding the implementation of prophylaxes in low-income countries is low adherence. This is due to the low education level of the patients and their parents, inadequacy of the home treatment and an absence of consistent availability of CFCs, when needed.

In our study, compliance to prophylaxis was good, which is consistent with the literature recommending a minimum compliance rate of 85% for prophylaxis to be validated.[21] However, many interventions were made to facilitate compliance throughout this study, including the strengthening parental motivation and involving nurses to administer a close follow-up of compliance with injections, even if a single patient used home therapy.

The incidence of inhibitors in our study was within the values reported in the literature, ranging from 15% to 33% in patients with severe HA.[10] In studies including previously treated patients (PTPs) HA patients showed that rFVIII-Fc is not more immunogenic than other types of CFCs.[22,23] The beneficial effect of the rFVIII-Fc has been demonstrated in prophylaxis, especially at low doses.[24] The low risk of rFVIIIFc immunogenicity observed during clinical trials[11,12] was also confirmed by the ASPIRE extension study,[25] which assessed long-term efficacy and safety and observed that no inhibitors were detected in a population of 211 patients on prophylaxis after 3.2 to 3.9 years of a mean follow-up period. However, the PUP study showed similar inhibitor incidence over other products, 31.1% for all inhibitors and 15.6%, the high-titer inhibitor.[26]

The deleterious effect of anti-FVIII inhibitors is limited by the fact that the Fc fragment of the immunoglobulin G contains regulatory T-cell epitopes that protect the FVIIIFc molecules.[27] Despite these reassuring results, regular monitoring will continue to assess the risk of inhibitor occurrence, especially in this context, in which the means of treatment with these inhibitors are not always available.

However, the number of patients on prophylaxis is small (15) and the group is not very homogeneous. This is related to the difficulties of implementing prophylaxis in resource-limited countries for a variety of reasons, including the lack of social support from the authorities, the lack of availability of home treatment and the poor geographic and financial accessibility to care for the patient with hemophilia (PWH).

Thus, the inclusion of more patients would allow for a larger cohort and better statistical analysis of the results.

Conclusion

The study results suggest that LDP is more beneficial than OD treatment in reducing bleeding and improving musculoskeletal health and physical ability, without increasing the incidence of inhibitor development. It also demonstrates the difficulties in providing more patients with LDP, given the weakness of the healthcare system and the low geographic and financial accessibility to care.

Author contributions

S.D. designed and coordinated the study. SAT performed clinical and biological data collection and analysis. SD and SAT wrote the paper. MS, DS, ABS and BFF participated in collecting data, SD Conceptualization, Investigation, Methodology.

Conflicts of interest

The authors declare that they have no interests that might be perceived as posing a conflict of interest or bias.

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