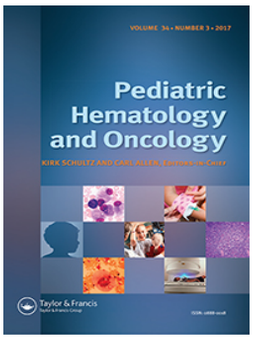

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Efficacy of standard prophylaxis versus on-demand treatment with bayer's sucrose-formulated recombinant FVIII (rFVIII-FS) in Chinese children with severe hemophilia A

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ABSTRACT

In China, care of patients with severe hemophilia primarily involves insufficient dosing of on-demand treatment and secondary low-dose prophylaxis (10 IU/kg 2× /wk). We sought to evaluate 3× /wk, standard-dose prophylaxis with sucrose-formulated recombinant factor VIII (rFVIII-FS; Bayer) compared with on-demand treatment in Chinese children with severe hemophilia A. Children and adolescents aged 2–16 years with severe hemophilia A, no inhibitors, and no prophylaxis for >6 consecutive months before study entry were eligible for this 24-week, interventional, sequential-treatment study. Patients received rFVIII-FS on demand for 12 weeks followed by a 12-week prophylaxis period (25 IU/kg 3× /wk). The primary efficacy endpoint was comparison of the annualized bleeding rate (ABR) of all bleeds in the prophylaxis versus on-demand phase. Additional variables included ABR of joint bleeds, school attendance/activity, daily activity, and hemophilia Joint Health Score (HJHS). Thirty patients (median age, 12 years) were treated and analyzed. Compared with on-demand treatment, prophylaxis reduced median (quartile [Q1; Q3]) ABR of all bleeds (57.5 [44.5; 73.9] vs 0 [0; 4.0]) and joint bleeds (34.5 [26.1; 56.5] vs 0 [0; 4.0]). Median (range) total HJHS improved after both the prophylaxis and on-demand phases (8.0 [0–48.0] and 11.0 [0–55.0], respectively) compared with baseline (16.0 [0–56.0]). School attendance/activity and daily activity improved with prophylaxis versus on demand. No inhibitors or treatment-related adverse events were reported. In this first prospective, standard-dose, secondary prophylaxis study in China, rFVIII-FS prophylaxis reduced bleeding and improved health outcomes versus on-demand treatment in children with severe hemophilia A.

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Introduction

Treatment of severe hemophilia A requires factor VIII (FVIII) replacement with plasma-derived or recombinant FVIII products. Patients may be administered FVIII products for the

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treatment of a bleeding event (on demand) or on a regular basis to prevent bleeding episodes (prophylaxis). Joint bleeding in patients with hemophilia A may result in progressive joint damage and arthropathy [1]. When started at an early age, prophylaxis has been shown to reduce bleeding and prevent hemophilic arthropathy compared with on-demand treatment [2,3]. Studies in adolescents and adults have reported similar bleeding and joint-related findings, as well as showing improved quality of life (QoL) with prophylactic treatment [4–7]. As a result of these data, FVIII prophylaxis is recommended by the World Federation of Hemophilia (WFH) and the National Hemophilia Foundation for treatment of patients with severe hemophilia A [8,9].

In China, primary prophylaxis is usually not possible because of a lack of adequate resources, particularly in rural areas [10,11]. As a result, joint outcomes and QoL are worse in China compared with developed countries in which primary prophylaxis is standard care [12,13]. Additionally, diagnosis of hemophilia A may be delayed for several years because of limited local medical care in rural areas [14]. Arthropathy is often present at an early age and becomes progressively worse with increasing age; a retrospective study showed that 91% of Chinese patients with hemophilia aged 6–9 years had evidence of arthropathy [13]. To improve the care of patients with hemophilia, the Hemophilia Treatment Centers Collaborative Network of China, which included a prophylaxis working group, was established in collaboration with WFH [11]. Two pilot studies have shown that low-dose FVIII prophylaxis (10 IU/kg twice weekly) reduced bleeding and improved joint function, school attendance/activity, and daily activity in Chinese patients aged 2–18 years with moderate or severe hemophilia A [15,16]. Nonadherence to prophylaxis was high overall, however, and varied by center, possibly related to differences in patient expectations and communication of the benefits of prophylaxis from the hemophilia treatment center [16]. Implementation of standard-dose prophylaxis (secondary or tertiary) in China and elsewhere may further reduce bleeding and improve joint outcomes in Chinese patients compared with currently available low-dose prophylaxis.

Prophylaxis with sucrose-formulated recombinant FVIII (rFVIII-FS; Kogenate® FS, Bayer, Berkeley, CA) has been shown to be safe and efficacious in children with severe hemophilia A [2,17]. Data from the Joint Outcome Study (JOS) showed that rFVIII-FS administered prophylactically (25 IU/kg every other day) was superior to on-demand treatment in preventing joint damage in young boys with severe hemophilia A [2]. Based on the JOS findings, rFVIII-FS was approved in China for prophylactic treatment in children; however, a study to demonstrate the superiority of rFVIII-FS prophylaxis versus on-demand treatment in Chinese patients was required post approval. We report the efficacy and safety results in Chinese children with severe hemophilia A treated with rFVIII-FS prophylactically (25 IU/kg 3 times per week) or on demand. This is the first interventional trial to evaluate standard secondary prophylaxis using rFVIII-FS in Chinese pediatric patients.

Patients and methods

Patients

Children and adolescents aged 2–16 years with severe hemophilia A (<1% FVIII:C) who were receiving on-demand treatment at screening and had no history of prophylaxis for >6 consecutive months before study entry were eligible for the study. Additional key inclusion criteria were ≥50 exposure days (EDs) with any FVIII product and no history of FVIII inhibitors.

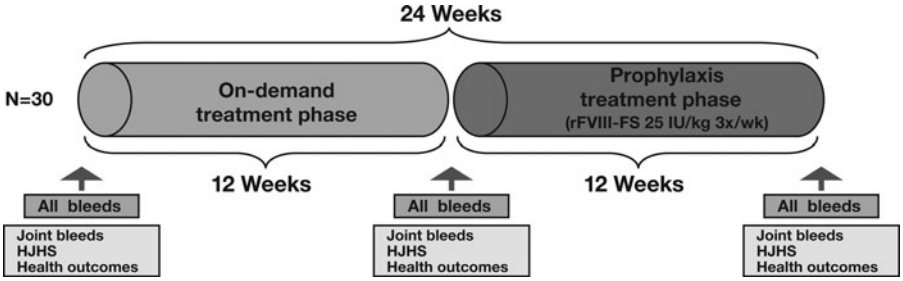

Figure 1. Study design. HJHS = Hemophilia Joint Health Score; rFVIII-FS = sucrose-formulated recombinant factor VIII. Arrows indicate in-hospital visit for study assessments.

Key exclusion criteria included any bleeding disease other than hemophilia A, thrombocytopenia (<100,000 platelets/mm^3), immunomodulatory agents during the study or 3 months before enrollment, requirement for premedication to tolerate FVIII infusions, renal impairment (serum creatinine >2.0 mg/dL), or liver disease.

Study design

This was a phase 4, prospective, multicenter, interventional, sequential-treatment study designed to evaluate the safety and efficacy of prophylactic treatment with rFVIII-FS compared with on-demand treatment in children with severe hemophilia A at 5 hemophilia treatment centers in China (ClinicalTrials.gov identifier: NCT01810666). Patients were treated on demand for 12 weeks (dose determined by physician) followed by a 12-week period during which patients received rFVIII-FS as prophylaxis at 25 IU/kg 3 times per week (Figure 1). A sequential-treatment design was used instead of a crossover design to avoid carryover effects from prophylaxis on subsequent on-demand treatment. Prophylaxis could be administered in the clinic or the patient's home. Informed consent was provided by the patient's parents or legal guardians, and the protocol was approved by each site's independent ethics committee/institutional review board.

Efficacy assessments

The primary efficacy endpoint was the annualized number of all bleeds during the prophylaxis phase compared with the on-demand phase; bleed data were recorded using patient diaries. Secondary variables were the annualized number of joint bleeds as well as joint function assessed before and after each study phase by the Hemophilia Joint Health Score (HJHS; score range, 0–124 [higher scores indicate worse joint health]) [18]. Physiotherapists who performed the HJHS were systematically trained and certified by the Hospital for Sick Children (Toronto, ON, Canada) [19]. All HJHS physiotherapists were blinded to patient treatment in this study. Additional predefined variables were school and daily activity and school attendance. School activity was measured using the Beijing Children's Hospital (BCH) scale, which ranged from 0 to 4 (higher score indicates more activity [0, unable to participate in activities beyond classes; 1, able to walk around in the school yard; 2, participates in exercise drills and stretching; 3, participates in noncontact sports such as swimming and jogging; and 4, participates in contact sports such as basketball but not in competition]). Similarly, the BCH scale (score range, 0–4) was used to measure daily activity (0, wheelchair bound; 1, able to walk slowly; 2, able to walk and participate in 1 activity such as swimming or jogging;

3, able to walk plus ≥2 additional activities; and 4, no activity limitations). School and daily activity and school attendance were assessed for the first 3 months before enrollment and at the end of each treatment phase.

Safety assessments

Safety variables were the incidences of all treatment-related and non-treatment-related adverse events (AEs) and serious AEs (SAEs). The development of an inhibitor (≥0.6 Bethesda units) was considered an SAE. Inhibitor testing was conducted at screening, at baseline, after the on-demand phase of the study, and at study completion. FVIII levels were assessed at screening and baseline.

Statistical analysis

Statistical analysis was performed using SAS software 9.2 or higher (SAS Institute Inc., Cary, NC, USA). Summary statistics were calculated for continuous data, and frequencies were calculated for categorical data. Annualized median rate and two-sided confidence intervals (CIs) of bleeding were calculated by applying Hodges-Lehmann estimates. The intent-to-treat (ITT) population (all patients for whom infusion and bleeding data were available) was used in the primary efficacy analysis. All patients treated with rFVIII-FS were included in the safety analysis. For intraindividual comparisons with 90% power, 18 patients were required to detect a difference of 30 in annualized joint bleeds (*SD*, 27). If the observed difference between treatments was 25% smaller than expected, 30 patients were required for 90% power. A subgroup analysis by patient age (<12 and ≥12 years) was also performed for demographics, disease characteristics, and annualized bleeding and joint bleeding.

Results

Study population

Thirty-three patients enrolled in the study, 3 of whom did not complete the screening (over recruitment per protocol, n = 1; screening failure, n = 2). The remaining 30 patients (ITT population) received rFVIII-FS, and all patients completed the study. The median (range) age was 12.0 (2–15) years; 14 patients were aged <12 years (Table 1). Prior on-demand treatment was divided between recombinant (16 patients [53.3%]) and plasma-derived (14 patients [46.7%]) products. The mean ± *SD* (median [range]) number of prestudy EDs was 110.8 ± 94.6 (98.5 [56–561]). At screening, target joints (defined as ≥3 bleeds in the same joint in 6 months) were identified in 22 patients (73.3%).

Table 1. Baseline demographics.

	Patients (N = 30)
Age, years	
Median (range)	12.0 (2—15)
Age groups, n	
<12 years	14
12–15 years	16
Target joints, n (%)	
Yes	22 (73.3)
Annualized number of all bleeds in last 3 months	
Median (range)	40 (8—144)
Annualized number of joint bleeds in last 3 months	
Median (range)	24 (4—120)

Table 2. Annualized bleeding rate for on-demand and prophylaxis treatment with rFVIII-FS.

Parameter	On-demand treatment phase (N = 30)	Prophylaxis treatment phase (N = 30)
All bleeds per year		
Median (Q1; Q3)	57.5 (44.5; 73.9)	0 (0; 4.0)
Mean ± SD	58.9 ± 16.6	3.0 ± 5.9
Joint bleeds per year		
Median (Q1; Q3)	34.5 (26.1; 56.5)	0 (0; 4.0)
Mean ± SD	39.5 ± 19.6	2.2 ± 4.7
Spontaneous bleeds per year		
Median (Q1; Q3)	43.4 (30.1; 53.4)	0 (0; 0)
Mean ± SD	41.8 ± 18.7	1.8 ± 4.4
Trauma-related bleeds per year		
Median (Q1; Q3)	14.7 (0; 30.8)	0 (0; 0)
Mean	17.0 ± 16.3	1.2 ± 2.5

rFVIII-FS = sucrose-formulated recombinant factor VIII; Q1 = quartile 1; Q3 = quartile 3.

The median (range) study duration was 80.0 (59.0–94.0) and 91.5 (79.0–100.0) days for the on-demand and prophylaxis phases, respectively. During the on-demand phase, patients accumulated a median (range) of 19.5 (6.0–37.0) EDs compared with 40.0 (34.0–45.0) EDs during the prophylaxis phase. During the prophylaxis phase, 1164 of the 1195 planned infusions were administered. The mean number of infusions per week increased from 1.8 during the on-demand phase to 3.1 during the prophylaxis phase. The median (range) dose for prophylactic treatment was 27.1 (22–45) IU/kg per infusion. Factor utilization was higher during the prophylaxis phase (median [range], 1068.62 [800.0–1818.2] IU/kg) compared with the on-demand phase (345.89 [85.1–966.7] IU/kg).

Efficacy

Annualized bleeding rate

The annualized bleeding rates (ABRs) for total, joint, spontaneous, and traumatic bleeds are shown in Table 2. Applying Hodges-Lehmann estimates for median and two-sided CIs, the annualized median bleeding rate for all bleeds was 58.0 (95% CI, 52.7–66.0) for the on-demand phase and 2.0 (95% CI, 0–3.8) for the prophylaxis phase. This equates to a >95% reduction in bleeds per year during the prophylaxis phase compared with the on-demand phase (median [95% CI] difference, 56.0 [48.8–62.5] bleeds). Using the same statistical calculations, the annualized median rate of joint bleeds was also substantially reduced from the on-demand to the prophylaxis phase (39.7 [95% CI, 30.5–46.9] vs 1.9 [95% CI, 0–2.0]) with >95% reduction in yearly bleeds observed (median difference [95% CI], 37.7 [30.4–46.0] bleeds).

Treatment of bleeds

The total number of bleeds was markedly reduced during the prophylaxis phase compared with the on-demand phase (22 vs 422; Table 3). Nineteen (63.3%) patients in the prophylaxis phase had 0 bleeds, whereas all patients in the preceding on-demand phase had ≥1 bleed. Joint bleeds were most common in both phases, with 57.2% and 35.7% of joint bleeds involving a target joint in the on-demand and prophylaxis phases, respectively. Most bleeds during the prophylaxis phase were mild, whereas most bleeds occurring during the on-demand phase were moderate (Table 3). Patient-reported response to the treatment of bleeds was good or excellent in 94% and 95% of all bleeds in the on-demand and prophylaxis phases, respectively. The median (range) number of all rFVIII-FS infusions to treat bleeds per patient in patients who bled was lower in the prophylaxis phase compared with the on-demand phase

Table 3. Bleed type and treatment of bleeds.

Parameter, n (%)	On-demand treatment phase (N = 30)	Prophylaxis treatment phase (N = 30)
Bleed type	422 (100.0)	22 (100.0)
Joint	282 (66.8)	16 (72.7)
Muscle	77 (18.2)	1 (4.5)
Skin/mucosa	57 (13.5)	4 (18.2)
Internal	3 (0.7)	1 (4.5)
Other	3 (0.7)	0 (0)
Severity of bleed*	422 (100.0)	22 (100.0)
Mild	193 (45.7)	14 (63.6)
Moderate	212 (50.2)	7 (31.8)
Severe	17 (4.0)	1 (4.5)
Infusions to treat bleeds	422 (100.0)	22 (100.0)
≤1	288 (68.2)	18 (81.8)
2	88 (20.9)	1 (4.5)
3	16 (3.8)	2 (9.1)
>3	30 (7.1)	1 (4.5)

*Mild bleeds were defined as superficial skin bleeds, oral bleeds, or very early joint or muscle bleeds with no or minimal swelling, little pain, and no or minimal motion restriction that occurred after 1 infusion; moderate bleeds were characterized by more intense pain as well as additional symptoms, such as motion restriction, swelling, or increased joint temperature; severe bleeds were characterized by intense pain with high motion restriction (almost no motion possible) and swelling, generally required >1 infusion, and took several days to resolve, or were life-threatening intracranial or intra-abdominal bleeds.

(1.0 [1.0–11.0] vs 19.5 [6.0–52.0]). This difference may be mostly attributed to the substantially greater number of bleeding episodes reported during the on-demand phase compared with prophylaxis (422 vs 22 bleeds, respectively), as mentioned above. Per bleed, the number of rFVIII-FS infusions administered for treatment of bleeds was similar in both phases (median [range], 1.0 [0–6.0] and 1.0 [0–7.0] for patients in the prophylaxis and on-demand phases, respectively). Most bleeds were treated with ≤2 infusions (Table 3). A higher median (range) dose was used for the treatment of bleeds in the prophylaxis phase compared with the on-demand phase (25.0 [11.5–35.7] vs 15.9 [7.4–25.0] IU/kg/infusion).

Subgroup analysis

The median (quartile [Q1; Q3]) ABR for total bleeds was similar for patients aged <12 years (n = 14) and ≥12 years (n = 16) in both the on-demand phase (59.2 [53.3; 76.3] and 56.4 [41.3; 73.1], respectively) and the prophylaxis phase (0 [0; 4.0] and (0 [0; 4.0]), consistent with the improved ABR observed during prophylaxis in the total population. Similarly, lower ABRs for joint bleeds were observed in both age groups in the prophylaxis phase compared with the on-demand phase (median [Q1; Q3], 0 [0; 4.0] and 0 [0; 4.0] vs 31.8 [26.1; 53.4] and 42.0 [26.0; 59.1] for patients aged <12 and ≥12 years, respectively).

Joint function and health outcomes

Joint health improved in both phases of the study compared with baseline (Table 4). Median (range) total HJHS improved after the on-demand phase compared with baseline (11.0 [0–55.0] vs 16.0 [0–56.0]) with continued improvement after the prophylaxis phase (8.0 [0–48.0]). The median difference at the end of each phase compared with the beginning was −4.0 and −2.0 for on demand and prophylaxis, respectively. Similarly, the joint-specific HJHS also improved in both phases (median difference at the end of each phase was −4.0 and −1.5 for on demand and prophylaxis, respectively). Mean joint function for total and joint-specific HJHS also improved in both phases (Figure 2).

Patients were absent from school fewer days in both phases of the study (mean ± *SD*, 1.8 ± 3.6 and 0.2 ± 0.6 days for on demand and prophylaxis, respectively) compared with

Table 4. Hemophilia joint health score after on-demand and prophylaxis treatment phases.

Parameter	Baseline (n = 29)	On-demand treatment phase (N = 30)	Prophylaxis treatment phase (N = 30)
Total HJHS*			
Mean ± SD	16.3 ± 13.7	13.2 ± 13.5	10.0 ± 11.5
Median (range)	16.0 (0–56.0)	11.0 (0–55.0)	8.0 (0–48.0)
Mean difference ± SD†		−3.1 ± 12.6	−3.20 ± 6.6
Median difference (range)†		−4.0 (−24.0 to 54.0)	−2.0 (−27.0 to 7.0)
Joint-specific HJHS‡			
Mean ± SD	14.6 ± 12.3	11.9 ± 12.5	9.0 ± 10.3
Median (range)	14.0 (0–52)	10.5 (0–53)	6.5 (0–44)
Mean difference ± SD†		−2.7 ± 12.0	−2.8 ± 6.3
Median difference (range)†		−4.0 (−20.0 to 53.0)	−1.5 (−27.0 to 7.0)

HJHS = Hemophilia Joint Health Score.
*Higher HJHS scores indicate worse joint health.
†Difference from start to end of each period (n = 29 for on-demand treatment, n = 30 for prophylaxis).
‡Joint-specific HJHS = total score – global gait score.

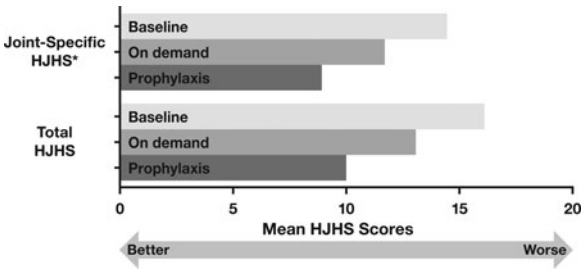

Figure 2. Hemophilia Joint Health Scores (HJHS) after prophylaxis and on-demand treatment phases. *Joint-specific HJHS = total score – global gait score. Mean HJHS scores (total and joint specific) at baseline and following the prophylaxis and on-demand treatment phases are shown.

the 3 months before enrollment (9.4 ± 10.5 days). School and daily activity scores improved more during the prophylaxis phase than the on-demand phase (Table 5 and Figure 3), and both were improved compared with 3 months before enrollment (data not shown).

Table 5. Health outcomes during the on-demand and prophylaxis treatment phases.

Parameter	On-demand treatment phase	Prophylaxis treatment phase	Intraindividual difference*
Days absent from school	n = 29	n = 29	
Mean ± SD	1.8 ± 3.6	0.2 ± 0.6	1.6 ± 3.6
Median (range)	0 (0 to 16.0)	0 (0 to 2.0)	0 (−2.0 to 16.0)
School activity score	n = 29	n = 29	
Mean ± SD	1.8 ± 1.0	2.5 ± 1.3	−0.7 ± 1.2
Median (range)	2.0 (0 to 3.0)	3.0 (0 to 4.0)	0 (−3.0 to 2.0)
Daily activity score	n = 30	n = 30	
Mean ± SD	2.0 ± 1.0	3.1 ± 1.1	−1.1 ± 1.3
Median (range)	2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)	−1.0 (−3.0 to 1.0)

*Difference in values between on-demand and prophylaxis treatment phases.

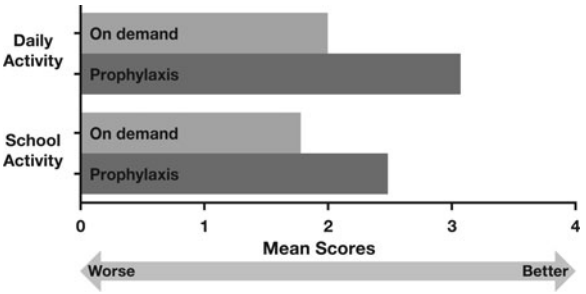

Figure 3. School activity and daily activity score after prophylaxis and on-demand treatment. Mean values for school and daily activity scores following the two treatment phases are depicted.

Safety

Treatment-emergent AEs were reported in 8 (26.7%) patients during the study, all of which resolved during the study. All AEs were mild or moderate, and none were related to rFVIII-FS treatment. No SAEs were reported, and no patients developed inhibitors.

Discussion

In this phase 4 study, standard-dose secondary prophylaxis with rFVIII-FS administered 3 times per week resulted in a greater reduction in total and joint bleeds compared with on-demand treatment in Chinese children with severe hemophilia A. After 12 weeks of prophylaxis 3 times per week, median ABRs were 0 for total, joint, spontaneous, and traumatic bleeds. Most patients (63%) treated with prophylaxis had 0 bleeds, and, for those who did experience a bleeding event while receiving prophylaxis, most of the bleeds were mild. In contrast, all patients treated on demand had ≥1 bleeding event, most of which were moderate in severity. Regardless, similarly high percentages of patients in the on-demand (94%) and prophylaxis (95%) phases reported good or excellent response to treatment of bleeds, and most bleeds in both treatment phases were treated with ≤2 infusions. Joint health improved during the on-demand phase compared with baseline and continued to improve during the prophylaxis phase. Similarly, school and daily activity scores improved in both phases of the study compared with 3 months before enrollment and were highest after the prophylaxis phase. The improved outcomes in both phases of the study compared with baseline underscores the suboptimal standard of care that is currently available for patients with hemophilia A in China. Because of limited resources, doses used for on-demand treatment in routine clinical practice in China are much lower compared with the doses used for on-demand treatment in the study. The ABR estimated from the 3 months prior to study entry appears to be lower than the ABR for the on-demand phase of the study. However, it is likely that the prestudy ABR was underestimated because it was based on patient recall, whereas bleed data during the study were collected using a patient diary.

In the present study, 97% of the expected total numbers of infusions during the prophylaxis phase were administered, indicating good treatment adherence, which may have contributed to the improved outcomes compared with baseline. Treatment with rFVIII-FS was well tolerated in this study: all AEs were mild or moderate (and none were related to rFVIII-FS), and no patients developed inhibitors. It is noteworthy that all patients who started treatment completed the study. This is in contrast with the 35% completion rate reported in a previous multicenter pilot study in China that consisted of an 8-week observation period during

which patients were treated on demand followed by a 6- to 12-week period of secondary prophylaxis (10 IU/kg twice weekly) [16]. Centers in the low-dose prophylaxis pilot study cited perceived lack of benefits of prophylaxis in patients/parents, inconvenience of frequent visits for infusions, and lack of a specialized staff as reasons for low adherence in their study [16]. In our study, prophylaxis could take place in the patient's home, which may have alleviated the inconvenience of frequent trips to the center. It is also possible that the staff at the centers in our study were experienced at communicating the benefits of prophylaxis to patients and parents. The use of prophylaxis in China has expanded since the first low-dose prophylaxis study. As a result, patients and parents are more aware of the benefits of prophylaxis, which may have contributed to increased adherence in our study.

The present study is the first in China to evaluate prophylaxis using a standard dose. Whereas prophylaxis is recommended by the WFH as standard care for patients (particularly children) with severe hemophilia A [8], limited resources in China have prevented the adoption of standard-dose primary prophylaxis regimens. Joint bleeding and subsequent joint damage occurs in many patients before they receive any type of treatment, thus eliminating the possibility of primary prophylaxis [13], Studies in the United States and Europe have shown that secondary prophylaxis with standard doses (20–40 IU/kg 3 times per week) may be effective in patients with established joint bleeds [4,7,20,21]. In developing countries with resource constraints, frequent administration of lower doses of prophylaxis may be an effective option [8]. A multicenter pilot study with low-dose (10 IU/kg rFVIII-FS twice weekly) secondary prophylaxis in Chinese children with moderate to severe hemophilia A demonstrated reduced bleeding and improved daily activity compared with patients treated on demand [16].

The findings from this study are consistent with previous randomized controlled studies that demonstrated the benefit of prophylaxis in children using similar dosing regimens [2,3]. In these studies, prophylaxis was initiated at a younger age compared with the present study, in which the median age was 12 years. Despite the relatively delayed time to the initiation of prophylaxis, the benefits of prophylaxis were clear in our trial: patients with established joint bleeds benefited from standard-dose prophylaxis. This is important in a developing country such as China where it is currently difficult to initiate prophylaxis regimens in children at a young age before joint damage occurs. This study will also contribute to an update of the Expert Consensus on Hemophilia Diagnosis and Treatment in China, which will further help advocate for standard-dose prophylaxis in China.

The relatively short observation period (3 months for prophylaxis) because of limited resources was a limitation of this study. A longer observation period could lead to more substantial differences in the efficacy of prophylaxis versus on-demand treatment; however, clinically important improvements were observed despite the relatively short study duration. Also, no randomization was performed in this study; considering the short observation period and small sample size, the sequential treatment design was more feasible.

Conclusions

In this first study in China of standard 3-times-weekly prophylaxis, rFVIII-FS prophylaxis was associated with reduced bleeding, improved joint function, and improved health outcomes compared with on-demand treatment in children with severe hemophilia A. Three-times-weekly prophylaxis with rFVIII-FS was well tolerated, with no SAEs or inhibitors reported in the study. The current results confirm the previously reported benefits of prophylaxis in children, both in China [15,16] and elsewhere [2,3].

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Conflict of interest disclosure

Y. Zhao, J. Xiao, R. Yang, R. Wu, Y. Hu, and J. Sun have no conflicts of interest to declare. H. Beckmann is an employee of Bayer AG. J. Wu and Q. Hou are employees of Bayer.

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