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Review Article

Inhibitors and prophylaxis in paediatric haemophilia patients: Focus on the German experience

Karin Kurnik [a,*], Günter Auerswald [b], Wolfhart Kreuz [c]

[a] Zentrum für Pädiatrische Hämostaseologie, Ludwig-Maximilian Universität, Klinikum der Universität, Campus Innenstadt, Lindwurmstraße 4, 80337 München, Germany
[b] Prof. Hess Kinderklinik, Klinikum Bremen Mitte, Bremen, Germany
[c] HZRM – Hämophilie-Zentrum Rhein Main, Mörfelden-Walldorf, Germany

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ABSTRACT

Prophylaxis is now an established treatment standard in haemophilia in Western Europe and the US with multiple studies demonstrating the clinical benefits of prophylaxis over on-demand treatment. In Western Europe in particular, prophylactic use of factor VIII (FVIII) is high as a result of the findings from the early prophylaxis studies and adherence to national guidelines. Unfortunately, prophylaxis has not yet been implemented on a worldwide basis. The introduction of prophylaxis by haemophilia treatment centres in Bremen, Frankfurt and Munich, as recommended in German guidelines, has significantly improved outcomes for our young haemophilia patients. In the Frankfurt centre, a decreasing rate of inhibitors has been observed since prophylaxis was started early, dosing was individualized, and the importance of treatment continuity was recognized. The centres in Munich and Bremen have explored the possibility of further reducing inhibitor rates using early tolerization – a new prophylaxis regimen that introduces low FVIII doses administered once weekly as soon as a bleeding tendency is observed – with excellent results. All three centres avert the induction of immunological danger signals by avoiding the use of central venous catheters, postponing vaccination wherever possible and not undertaking elective surgery during the early FVIII exposure days. The benefits of using this approach have been confirmed by the remarkably low rates of inhibitors in previously untreated patients reported at these centres. Hopefully, as we and others explore new prophylaxis regimens for our paediatric patients, we can work towards the goal of one day overcoming this serious complication of haemophilia treatment.

Contents

Abbreviations: AHF, antihaemophilic factor; APC, antigen presenting cell; b.w., body weight; FVIII, factor VIII; ICH, intracranial haemorrhage; OR, odds ratio; PAMP, pathogen-associated molecular pattern; pdFVIII, plasma-derived factor VIII; rFVIII, recombinant factor VIII; PRR, pattern recognition receptor; PUP, previously untreated patient; RODIN, Research Of Determinants of INhibitor Development among PUPs with haemophilia.

* Corresponding author. Tel.: +49 89 5160 2853; fax: +49 89 5160 4453.
E-mail address: Karin.Kurnik@med.uni-muenchen.de (K. Kurnik).

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Introduction

The optimal management of patients with haemophilia is complex and requires the provision of preventive care, the prompt and appropriate use of replacement therapy for acute bleeding episodes, as well as for prophylaxis, and the treatment of complications. Patients

Table 1
Early publications (1942–1994) on the use of prophylaxis in haemophilia.

Research group	Patients (N)	Study period	Type of FVIII	Schedule	Outcome
Johnson [1]	5	NA	Lyo. human plasma	NA	Tooth extractions were possible
Alexander et al. [2]	4	21, 19, 13, and 10 months	Human plasma	1×/d; 2×/d; 3×/wk; 4×/wk;	Bleeds reduced
Nilsson et al. [3]	3 HA	1958–1961	Fraction I–0	Prophylaxis 0.5 Fraction I-0/month	Deformity avoided
Ahlberg [4]	8 HA	1–7 years	AHF conc.	Half dose every 2nd–4th week	Severe into moderate HA
Pool et al. [5]	2 HA		Cryo.	3 intramuscular applications	Efficacy not sufficient
Robinson et al. [6]	1 HA	3 months	Cryo.	Every 12 hours	No bleeds
Shanbrom et al. [7]	1 HA	12 months	AHF conc.	Once/wk	No bleeds
Van Creveld [8]	2 HA	12–15 months	Cryo.	1–3–7×/wk	Prevention of joint damage
Hirschmann et al. [9]	4 HA	2–24 months	Cryo.	QOD; 4×/wk; 5×/wk;	Fewer bleeds
Kasper et al. [10]	5 HA		AHF conc.	250 IU/FVIII/day; 2,000 IU/wk; 1,500 U 3×/wk; 500 IU/daily	Less bleeds the higher the FVIII administered
Nilsson et al. [11]	24 HA	1–10 yrs	AHF conc.	100 mL every 2–4 wks	Bleeds reduced and less severe; no inhibitors
Ramsay et al. [12]	2 HA, 1 HB	9 months	Cryo. HA; FII-IX-X conc. HB	Six pack cryo. once/wk HA; two vials of FII-IX-X conc.	HB improved; HA felt better
Morfini et al. [13]	10 HB	12 months	FIX conc.	7.5 IU/kg 2×/wk; 15 IU/kg/wk	Bleeds reduced; bi-weekly superior
Aronstam et al. [14]	4 HA	Two school terms	Cryo.; Kryobulin	2×/wk to raise FVIII to 15% or 30% of average normal	Reduction of bleeds
Nilsson et al. [15]	52 HA,8 HB	Since 1958	FVIII conc.	24–40 IU/kg 3×/week HA; 25–40 IU/kg 2×/week HB	Prevented haemophilic arthropathy if started early
Aledort et al. [16]	323 HA	6 years	FVIII conc.	From 0 to >2,000 IU/kg/yr	High dose regular prophylaxis started at very young age can preserve integrity of haemophilia joints

AHF, antihaemophilic factor; conc., concentrate; Cryo., cryoprecipitate; d, day; FII, factor II; FVIII, factor VIII; FIX, factor IX; FX, factor X; HA, haemophilia A; HB, haemophilia B; IU, international unit; Lyo., lyophylized; NA, not available; QOD, every other day; wk, week; yr, year.

with inhibitors are at greater risk of difficult-to-treat complications, such as haemophilic arthropathy, which may impact their quality of lives. The utility of prophylaxis in not only preventing life-threatening bleeds, particularly intracranial haemorrhages (ICH), but also in preserving joint and musculoskeletal function, particularly in young haemophilia patients, and also in preventing inhibitor development, clearly supports a role for prophylaxis in the long term. In fact, there is now broad consensus that prophylaxis should be provided to all young haemophilia patients. However, the optimal dose and regimen at the start of prophylaxis remain unclear. This article discusses prophylaxis and inhibitors in paediatric haemophilia patients with a particular focus on our experiences in Germany.

Prophylaxis Through the Years: a Brief History

The first reports on the prophylactic use of normal human plasma in haemophilia patients were published in the 1940s by Johnson [1] and Alexander and Landwehr [2]. Irmgard Nilsson and her group from Sweden led the way in Europe by introducing the concept of prophylaxis in haemophilia A and demonstrating that prophylactic use of antihaemophilic factor (AHF) could decrease the frequency of severe bleeding episodes and essentially convert a severe form of the condition into a moderate form [3,4]. Other early publications describing prophylaxis in haemophilia patients are shown in Table 1 [1–16].

The studies by Nilsson et al. used relatively low dosages of FVIII (e.g. human fraction I-0) administered once every 14 days [3]. This evolved over the years to treatment every 2–4 weeks [11] and then to the use of 25–40 IU FVIII/kg body weight (b.w.) three times a week [15]. The incidence of clinically relevant inhibitors appeared to remain low over the years (8% in 1970; 7.5% in 1992); however, laboratory screening for inhibitors was not as intensive at the time of these studies as it is today.

Use of prophylaxis in Germany has been documented by several groups [17–20]. Brackmann et al. summarized their experiences with prophylaxis in 1992 [21]. This group began using prophylaxis in 1973 and, in 1978, they initiated a controlled study involving 90 patients with severe haemophilia A, adjusting prophylactic regimens to the individual needs of each patient using clinical and radiological assessments [17,21]. Over a 12-year period of treatment follow-up, the clinical scores of most knee and ankle joints remained unchanged, although a few worsened and a few improved [21].

Schimpf et al. investigated different prophylaxis patterns in six of their patients with severe haemophilia A over a period of 18 months and found that, with more frequent intervals of FVIII administration, bleeding stopped [18]. Doses of 36 IU FVIII/kg b.w. once a week were found to be less effective than 18 IU/kg b.w. twice a week and 12 IU/kg b.w. three times a week; the three-times-weekly regimen produced the best results, with no further bleeding episodes despite the fact that patients continued to work. Prior to prophylaxis, 35 bleeds over a period of 2 months had been reported in these individuals [18].

Schramm summarized the experience with prophylaxis in several cohorts of European patients and identified the need to individualize treatment for each individual [20]. Prophylaxis was recommended for children and adults experiencing more than 2–3 bleeding episodes per month, for very active individuals and those whose bleeding episodes were affecting their education or career, for patients after surgery for a limited time, in patients undergoing intensive physiotherapy, and in those who requested it.

Aledort et al. subsequently evaluated the physical and radiological data from 477 young patients (aged <25 years) with severe haemophilia A over a period of 6 years and concluded that full-time prophylaxis was more important than the use of higher on-demand doses of FVIII to achieve a good orthopaedic outcome [16].

Another important paper on prophylaxis and the optimal time to start treatment was published by Kreuz et al. in 1998 [19]. This group summarized their experiences of treating three different cohorts over