

Commentary: “Rapid Report – Treatment of Hemophilia Patients”

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Background

Hemophilia is a rare hereditary bleeding disorder caused by a deficiency of coagulation factors, which are necessary for hemostasis. The characteristic phenotype is the bleeding tendency. Hemophilia almost exclusively affects males since the mutated gene is located on the X chromosome^{1,2}.

Although the underlying genetic defect is so far incurable, gene therapy might be an alternative approach to the current treatment of hemophilia. Here, a single injection would induce a long-term production of the defecting clotting factor^{3,4}. Initial success of gene therapy has been shown in very small numbers of hemophilia patients in prior studies^{5,6} and also in preliminary results of phase 1/2 trials⁷⁻⁹.

Primarily, two subtypes are distinguished depending on the underlying mutation: a deficiency in coagulation factor VIII is referred to as hemophilia A whereas a deficiency in coagulation factor IX is referred to as hemophilia B. Hemophilia A is the most common type of hemophilia and represents about 80-85% of the total hemophilia population². Prevalence varies considerably among countries. The prevalence of hemophilia A per 100,000 males for high income countries is approximately 12.8 ± 6.0 (mean \pm standard deviation (SD)) and 6.6 ± 4.8 for the rest of the world¹⁰, the prevalence of hemophilia B per 100,000 males is about 2.7 ± 1.6 and 1.2 ± 1.3 , respectively¹¹. Hemophilia is categorized according to the clotting factor level in blood with three levels of severity comprising mild (>5 - $<40\%$ of normal activity), moderate (1 - 5%), and severe ($<1\%$)¹². In severe hemophilia, hemorrhaging is spontaneous and extensive, affecting joints and muscles and can, if not prevented through adequate treatment, result in permanent joint derangements, contractures, and the formation of pseudotumors^{1,2,13}. Some bleeds such as cerebral or gastric hemorrhages can be life-threatening and require immediate treatment².

Treatment strategies

Treatment of hemophilia patients essentially consists of substituting the missing coagulation factors^{1,14}. The primary treatment objectives are to prevent bleedings, to treat bleedings, their related complications and secondary damages, as well as to preserve joint function^{2,14}. Generally, there are two treatment strategies to replace clotting factors: prophylactically by replacing factor concentrates before occurrence and in order to prevent

bleeding; on-demand by administering factor concentrates subsequent to bleedings¹⁵.

Prophylaxis is the gold standard in children¹⁶. In adolescents and adults, the optimal therapy strategy is to some extent still under discussion as studies comparing prophylactic and on-demand treatment are limited and often have methodological limitations such as retrospective design, limited sample sizes and follow-up periods¹⁷⁻¹⁹. Additionally, expenses of prophylaxis compared to on-demand treatment must be considered since clotting factor consumption is about 2-3 times higher. In patients suffering from severe hemophilia A clotting factor consumption accounts for 83% of total costs²⁰. General recommendations on treatment strategies in hemophilia patients thus have high economic impact on healthcare systems and, therefore, should be grounded on best available evidence.

Benefit assessment of prophylactic versus on-demand treatment

A benefit assessment of prophylactic versus on-demand treatment of patients with severe hemophilia A and B was recently conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG)²¹. The IQWiG is a scientific institute responsible for assessing the quality and efficiency of medical interventions in the German statutory health insurance system, which covers about 85% of the German population. The institute is an independent organization which only accepts commissions from the Federal Ministry of Health and the Joint Federal Committee. IQWiG's reports constitute the basis for decisions on which procedures are reimbursed by statutory health insurances and, therefore, are of great significance for healthcare of the German population.

IQWiG's assessment on treatment of hemophilia is based on systematic literature searches in medical databases, study registries, and publicly available authorization documents. In order to also include unpublished study data, pharmaceutical manufacturers of drugs used in treatment of hemophilia patients approved for the German market were contacted as well. Randomized controlled trials (RCT) and prospective, non-randomized, parallel-group intervention studies, enrolling a minimum number of 50 patients were included. Treatment periods were required to have lasted at least 6 months in order for the study to be included. Overall, three studies fulfilled inclusion criteria: SPINART (Secondary Prophylaxis in Adults, a Randomized Trial), ESPRIT (Evaluation Study on Prophylaxis: a Randomized Italian Trial), and JOS (Joint Outcome Study). These studies are randomized, open-label, parallel-group trials which included severe hemophilia A patients. A summary of these studies is presented in table 1. With regards to hemophilia B, appropriate studies could not be identified by the IQWiG.

Description of studies included in the benefit assessment

SPINART²²⁻²⁶ enrolled 84 male adolescent and adult severe (factor VIII:C<1%) hemophilia A patients aged 12 to 50 years from 31 centers (USA, Romania, Bulgaria, Argentina) and randomized them 1:1 to prophylaxis or on-demand treatment (table 1). Participants completed a 6-week screening process followed by a 3-year treatment phase²⁵. Prophylaxis started at 25 IU/kg three times per week. In patients having ≥ 12 bleeding episodes per year, the dose could be increased by 5 IU/kg at the end of year 1 and year 2 to a maximum dose of 30 or 35 IU/kg, respectively. On-demand treatment was administered on the basis of investigator clinical recommendations²⁵. The primary efficacy endpoint was the number of total bleeding episodes in the intention-to-treat (ITT) population. This endpoint was analyzed after the last patient had completed one year of follow-up. Secondary endpoints were change in joint function (using MRI scale, Colorado Joint Assessment Scale, and Haemo-QoL-A physical functioning domain), change in health condition (using Euro-QoL-5D) and level of pain (using Short Form McGill Pain Questionnaire) from baseline, health-related quality of life (using Haemo-QoL-A), adverse events and presence of factor VIII inhibitors, which were assessed after the study period of 36 month²¹. Other endpoints were joint, spontaneous, and trauma-related bleedings. Bleeding episodes and associated data, and infusion-related health issues were recorded by patients or their parents; bleeding severity was self-rated by patients²⁵.

ESPRIT²⁷ enrolled severe hemophilia A (factor VIII:C<1%) children between 1 and 7 years from 12 centers in Italy. 23 patients were randomized to prophylaxis and 22 to on-demand treatment (table 1). After knowing their treatment assignment, 2 patients randomized to prophylaxis and 3 patients randomized to on-demand withdrew their consent. These patients did not allow using their data on clinical status and therefore could not be included in the ITT-analysis. Finally, 21 patients received prophylaxis and 19 patients on-demand treatment. The study was planned to last 10 years from time of enrollment of the first patient²⁷. Prophylaxis was administered at a dose of 25 IU/kg three times a week on non-consecutive days and on-demand treatment was administered at a dosage of 25 IU/kg or more, every 12-24 hours until complete resolution of the bleeding episode²⁷. In case of breakthrough bleeds in the prophylaxis arm, patients had to be treated with extra doses of concentrates in the same way. Treatments were administered by a family member at home. The study protocol allowed early change of the assigned treatment if it was deemed as not adequate by the supervisor (e.g., due to high frequency of bleeding episodes, development of a target joint defined as three bleeds in the same joint within 6 months, life-threatening hemorrhage,

Study	SPINART ²²⁻²⁶	ESPRIT ²⁷	JOS ²⁸⁻³⁰
Study design	RCT, open-label, parallel-group	RCT, open-label, parallel-group	RCT, open-label, parallel-group
Population	Male adolescents and adults with severe hemophilia A, N=84	Children with severe hemophilia A, N=45, 5 patients withdrew their consent after knowing their treatment assignment leaving N=40 patients receiving study treatment	Children with severe hemophilia A, N=65
Eligibility	Males, 12 to 50 years ^a , factor VIII:C<1%, ≥150 exposure days with any factor VIII product, no measurable factor VIII inhibitor activity or history, no prophylaxis for >12 consecutive months in the past 5 years, 6-24 documented bleeding events or treatments in the prior 6 months	1 to 7 years, factor VIII:C<1%, no measurable factor VIII inhibitors	Males, <30 months, factor VIII:C<2%, a history of 2 or fewer hemorrhages into each index joint, normal baseline joint imaging, no measurable factor VIII inhibitors, normal platelet count, normal joint motion
Exclusion criteria	Patients having bleeding disorders other than hemophilia A, thrombocytopenia, abnormal renal function or active hepatic disease, use of immunomodulatory agents in the preceding 3 months, absolute CD4 lymphocyte cell count of <200 cell mm ⁻³	Clinical radiologic signs of joint damage, no bleeding episodes in the prior 6 months, a history of ≥2 bleeding episodes in the same joint or muscle, concomitant severe chronic diseases or congenital skeletal malformations, likelihood of poor compliance with long-term follow-up	See "Eligibility"
Treatment regimen	Prophylaxis: n=42 with factor VIII (Octocog alfa) 25 IU/kg, three times per week; On-demand: n=42 with factor VIII (Octocog alfa) on the basis of investigator clinical recommendations	Prophylaxis: n=21 with factor VIII (Octocog alfa) 25 IU/kg, three times per week; On-demand: n=19 with factor VIII (Octocog alfa) ≥25 IU/kg, every 12-24 hours	Prophylaxis: n=32 with factor VIII (Octocog alfa) 25 IU/kg, every second day; On-demand: n=33 with factor VIII (Octocog alfa) 40 IU/kg at bleeding onset and 20 IU/kg at 24 and 72 hours after bleeding onset and every other day thereafter up to 4 weeks until resolution of pain and limitation of mobility
Primary outcome	Number of total bleeding episodes	Overall frequency of clinically significant bleeding events; Occurrence and severity of joint damages	Preservation of index-joint structure when participants were 6 years old
Secondary outcome	Annualized number of joint bleeding episodes; Annualized number of joint, spontaneous, and trauma-related bleeding episodes; Health condition ^b ; Pain ^b ; Joint function; QoL; Adverse events; Presence of factor VIII inhibitors	Frequency of hemarthroses; QoL; Adverse events; Presence of factor VIII inhibitors	Number of joint and other bleeding events; Life-threatening bleedings; Adverse events; Presence of factor VIII inhibitors
Location and study period	31 centers (USA, 23; Bulgaria, 3; Romania, 3; Argentina, 2); 03/2008-11/2013	12 centers in Italy; 12/ 1996-12/1999	14 centers ^b in the USA; 08/1996-04/2005
Study length	6 week screening process; 3 years treatment phase	10 year period from time of enrollment of first patient	Treatment until participants reached age of 6 years (± 3 months ^b)
Study findings			
Bleedings	Median annualized bleeding rate: 0 in prophylaxis group, 32.8 in on-demand group; IRR [95%-CI]: 15.2 [8.5; 27.2]; P<0.001 ^c ; Number of patients with bleeding episodes: 20 in prophylaxis group, 41 in on-demand group; IRR [95%-CI]: 0.02 [0; 0.18]; P<0.001 ^c ; Life-threatening bleedings: none in both groups; Median annualized joint bleeding rate ^b : 0 in prophylaxis group, 24.4 in on-demand group; P not given; Median annualized spontaneous bleeding rate ^b : 0 in prophylaxis group, 19.8 in on-demand group; P not given; Median annualized trauma-related bleeding rate ^b : 0 in prophylaxis group, 7.9 in on-demand group; P not given	Median annualized bleeding rate: 4 in prophylaxis group, 12 in on-demand group; P<0.01; Median number of total bleeding events per patient: 25 in prophylaxis group, 76 in on-demand group; P<0.01; Median annual rate of hemarthroses per patient: 1 in prophylaxis group, 5.5 in on-demand group; P not given; Life-threatening bleedings: none in both groups	Median annualized bleeding rate: 1.2 in prophylaxis group, 17.1 in on-demand group ^b ; P<0.001 ^c ; Median annualized rate of index-joint bleedings: 0.2 in prophylaxis group and 4.4 in on-demand group ^b ; P<0.001 ^c ; Life-threatening bleedings: 0 in the prophylaxis group, 3 in the on-demand group; P=0.238
Mortality	No deaths occurred	No deaths reported	No deaths occurred
Joint function	Patients without joint damages: 8 of 32 in prophylaxis group, 8 of 30 in on-demand group ^a , OR [95%-CI]: 0.92 [0.29; 2.86] ^c ; P=0.90 ^c	Patients without joint damages: 15 of 21 in prophylaxis group, 5 of 19 in on-demand group, OR [95%-CI]: 7.0 [1.78; 28.17] ^c ; P=0.004 ^c	Patients without joint damages: 24 of 32 in prophylaxis group, 14 of 33 in on-demand group, OR [95%-CI]: 4.07 [1.42; 11.71] ^c ; P=0.008 ^c

Change in health condition from baseline	Using VAS ^d , EuroQoL-5D: Prophylaxis vs. on-demand (N=35 per treatment group ^b): SMD (Hedges'g) ^c : 0.73 [0.25; 1.22]; P=0.003	Not investigated by study	Not investigated by study
Change in level of pain from baseline	Average level of pain during preceding 4 weeks: using VAS ^d , SF-MPQ: prophylaxis vs. on-demand (N= 35 per treatment group ^b): SMD (Hedges'g) ^c : -0,71 [-1.19; -0.22]; P=0.003; Current level of pain: using NRS ^e , SF-MPQ: prophylaxis (N=35) vs. on-demand (N=34) ^b : SMD (Hedges'g) ^c : -0,55 [-1.03; -0.07]; P=0.026	Not investigated by study	Not investigated by study
Change in QoL from baseline	Using Haemo-QoL-A (total score): prophylaxis (N=41) vs. on-demand (N=42) ^b : SMD (Hedges'g) ^c : 0.56 [0.12; 1.00]; P=0.012	Assessed, but no analyzable data presented (e.g., baseline data not collected, number of respondents not given)	Not investigated in study
Inhibitors	No patients developed factor VIII inhibitors	Inhibitors: 3 in prophylaxis group, 2 in on-demand group; prophylaxis vs. on-demand OR [95%-CI]: 1.42 [0.21; 9.55] ^c ; P=0.766 ^c	Inhibitors: 4 in prophylaxis group, 5 in on-demand group; prophylaxis vs. on-demand OR [95%-CI]: 0.80 [0.19; 3.29] ^{b,c} ; P=0.825 ^c

^aThe youngest actually included patient was aged 15 years.

^bData extracted from clinical study reports of manufacturers.

^cCalculation conducted by IQWiG.

^dRating of pain intensity ranging from 0 to 100. Negative change indicates decrease of pain intensity.

^eRating of pain intensity ranging from 0 to 5. Negative change indicates decrease of pain intensity.

Abbreviations:

CI: confidence interval; QoL: quality of life; IRR: incidence rate ratio; IU: international units; NRS: numerical rating scale; OR: odds ratio; SF-MPQ: Short Form McGill Pain Questionnaire; SMD: standardized mean difference; VAS: visual analogue scale; vs: versus

Table 1: Studies included in IQWiG's assessment comparing prophylaxis versus on-demand treatment using factor concentrates in children, adolescents, and adults with hemophilia A

or bone or cartilage damage on joint imaging)²⁷. In total, 5 patients in the on-demand arm and 4 patients in the prophylaxis arm switched treatment. The primary efficacy endpoint was the overall frequency of clinically significant bleeding events and the occurrence and severity of joint damages (determined using plain-film radiography). Bleedings and associated data such as time and site were documented by caregivers. Documentations were reviewed every 3 months²⁷. Secondary endpoints were frequency of hemarthroses, inhibitor development, quality of life, and adverse events (table 1).

JOS²⁸⁻³⁰ enrolled 65 severe hemophilia A (factor VIII:C≤2%) male children <30 months from 15 US centers and randomized 32 patients to prophylaxis and 33 patients to on-demand treatment (table 1). Children in the prophylaxis group received 25 IU/kg every other day. In case of hemarthroses, patients were treated with 40 IU/kg and the assigned prophylaxis schedule was resumed next day. The on-demand group was treated at the time of clinically recognized joint hemorrhage. On-demand treatment was administered at a dosage of 40 IU/kg at the time of joint hemorrhage and 20 IU/kg at 24 and 72 hours after the first dose and every other day thereafter up to four weeks until resolution of pain and impairment of mobility²⁹. The study protocol allowed for early termination of participation if the assigned treatment was inadequate for the child (e.g., development of inhibitors, bone or cartilage damage, and life-threatening bleedings)²⁹. The primary outcome

was preservation of index-joint structure (using MRI and plain-film radiography) when participants were 6 years old. Secondary outcomes were number of joints and other bleeding events. Bleedings were documented by means of telephone interviews with patients or parents. Adverse events and presence of inhibitors were also assessed.

Key results

IQWiG's assessment is based on the evaluation of the following end-points: severe and life-threatening bleedings, mortality, health condition, pain, joint deterioration, health-related quality of life, and adverse drug reactions such as inhibitors, infections, and thrombosis. Bleeding events and the prevention of bleedings were defined as independent patient-relevant end-points; they were explicitly not defined as a surrogate endpoint for joint damages³¹.

Bleedings

The benefit assessment indicates that prophylactic treatment is superior to on-demand treatment for all age-groups regarding the end-point severe bleedings²¹ (table 1).

The SPINART study shows a significant reduction in bleedings for adolescents and adults with prophylaxis. The median annualized bleeding rate was 0 with prophylaxis and 32.8 with on-demand after 12 months. Patients treated on-demand experienced nearly 15 times as many bleeding episodes compared with patients treated prophylactically²⁶.

The number of patients with bleeding episodes after 12 months was 20 in the prophylaxis group and 41 in the on-demand group. However, the IQWiG identified a high risk of bias due to the open-label outcome assessment and due to the fact that bleedings were documented by the patients themselves.

These results are consistent with recent study findings for severe hemophilia A patients. The POTTER study (Prophylaxis Versus On-demand Therapy Through Economic Report), an observational, prospective, open-label, multicentre trial, evaluated 27 patients with long-term late secondary prophylaxis and 26 with on-demand treatment over a period of >5 years³². Eligible patients were aged 12 to 55 years, male, had no measurable factor VIII inhibitors, and received prophylaxis or on-demand therapy within the prior six months. Patients were enrolled on their current treatment regimen and stratified by age into the subgroups 12-25 and 26-55 years. Patients receiving prophylaxis experienced significantly less total bleeding episodes as compared with on-demand treatment (annualized bleeding rate 2.54 versus 19.77 in patients aged 12-25 years and 2.95 versus 21.49 in patients aged 26-55 years).

As regards children, in ESPRIT the rate of severe bleeding episodes was 4 per child and year with prophylaxis and 12 with on-demand. Results of the JOS study show 1.2 major bleedings for prophylactic and 17.1 for on-demand treatment regimens (table 1). However, regarding both pediatric studies the IQWiG identified a high risk of bias due to several methodological limitations such as the high drop-out rates and crossovers. For example, in ESPRIT only 43% of patients receiving prophylaxis and 36% receiving on-demand ended therapy as originally intended. Additionally, 5 patients refused treatment after randomization and presented study results based on analysis of the remaining 40 patients. Furthermore, IQWiG recognized risk of bias in the documentation of bleeding episodes, which was conducted in ESPRIT by patients or parents using diaries and in JOS by means of telephone interviews with patients or parents.

In spite of the methodological limitations of the included studies, the substantial differences regarding bleeding episodes, which cannot solely be a consequence of study bias, indicate an additional benefit of prophylaxis to on-demand treatment²¹.

Differences concerning life-threatening bleeding episodes (e.g., brain, internal organs) were not present (SPINART) or could not be assessed since studies lacked sufficient data (ESPRIT and JOS).

Mortality

IQWiG could not assess potential differences between

prophylaxis and on-demand treatment in mortality since in SPINART and JOS no deaths occurred and ESPRIT did not report data for analysis.

Joint deterioration

Regarding joint deterioration, SPINART did not show significant differences between treatment groups (table 1). In ESPRIT joint damages have been found in 29% in the prophylaxis group and in 74% in the on-demand group and in JOS in 25% and 58%, respectively (table 1). However, this endpoint was assessed by imaging techniques such as radiography and MRI. Since validation studies are lacking, which show a clear correlation concerning severity of joint deterioration assessed by evaluation of imaging techniques and clinical symptoms, this endpoint was not accepted by the IQWiG and thus no conclusion concerning additional benefits was drawn.

Health condition, pain, and health related quality of life

For adolescents and adults, data of SPINART show additional benefits of prophylaxis concerning health status and pain within the preceding 4 weeks, while in both studies enrolling children with hemophilia A, this outcome was not investigated (table 1). However, due to methodological limitations in SPINART, the IQWiG concluded only a minor benefit of prophylactic as compared to on-demand treatment. Risk of bias was attributed to the open-label outcome assessment and the violation of the ITT principle since only 35 of 42 patients (83%) in both treatments arms were analyzed without replacing missing values²¹. Regarding health related quality of life, the benefit assessment showed statistically significant but non-relevant advantages of prophylactic treatment in SPINART. ESPRIT did not present sufficient data and JOS reported no data for further analysis (table 1).

Adverse events and inhibitors

Regarding adverse events and inhibitors, IQWiG concluded that no significant differences between study groups are present (SPINART) or studies did not present adequate data for further analysis (ESPRIT and JOS)²¹ (table 1).

Hemophilia B

With regards to hemophilia B, no study was identified and therefore no analysis conducted. These results do not imply that there is no difference between both treatment regimens; they rather imply the need for further research using RCT study design.

Conclusion

Prophylaxis is the gold standard in hemophilia

treatment of children and there is still debate about whether adults benefit as well. The IQWiG's benefit assessment is an important contribution to that debate as it indicates additional benefits of prophylaxis in hemophilia A patients as compared to on-demand-treatment not only in children but also in adolescents and adults: patients treated prophylactically experienced significantly less bleedings than patients treated on-demand. The assessment further indicates that prophylaxis has additional benefits concerning health status and pain in the group of adolescents and adults. Despite several methodological limitations of included studies, the substantial differences in bleeding episodes indicate that prophylaxis in severe hemophilia A patients is superior to on-demand treatment. These findings represent a clear indication for physicians and payers for prophylaxis in patients with severe hemophilia A.

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