Article published online: 2022-10-26

A Cross-sectional Analysis of Treatment in PUPs in 2021 in Germany – First Data from the GEPHARD Study Group

The GEPHARD Investigators

Hamostaseologie 2022;42(S1):S24–S31.

Address for correspondence Christoph Königs, MD, PhD, Department of Paediatrics and Adolescent Medicine, University Hospital Frankfurt, Goethe University, Theodor-Stern-Kai 7, 60596 Frankfurt am Main, Germany (e-mail: info@gephard.de; christoph.koenigs@kgu.de).

Christoph Bidlingmaier, MD, Hämophiliezentrum München – Bereich Pädiatrie, Dr. v. Haunersches Kinderspital, München, Deutschland (e-mail: info@gephard.de; Christoph.Bidlingmaier@med.uni-muenchen.de).

Abstract

Objectives Initial treatment in patients with haemophilia remains challenging. The choice of therapy, timing, dose and frequency have been and are still under intense debate. New treatment options like novel factor concentrates and non-factor therapies broaden the discussion.

Design The German Paediatric Haemophilia Research Database (GEPHARD) is a multicentre prospective observational study including children and adolescents with haemophilia A or B (FVIII or FIX levels <25 IU/dL) in a German treatment centre after January 1st, 2017. A cross-sectional analysis was performed in June 2021.

Results 249 children and adolescents from 22 participating centres in Germany were analysed in this cross-sectional analysis. 203 patients suffered from haemophilia A (PwHA) and 46 from haemophilia B (PwHB). The median age at diagnosis for Pw severe HA or HB was 6 or 2 months, the median age at analysis was 33 or 35 months for Pw severe HA or B, respectively. 117 Pw severe HA received treatment, including plasma derived concentrates (n = 43), standard recombinant concentrates (n = 23), extended half live concentrates (n = 33) and non-replacement therapies (n = 18). For Pw severe HB, plasma derived concentrates (n = 3), standard recombinant concentrates (n = 8) and extended half live concentrates (n = 14) were used. Current inhibitors were reported in 16 PwHA and 1 PwHB.

Conclusions GEPHARD was successfully established as a national cohort for newly diagnosed PwH in Germany. Epidemiological and treatment data were presented. Longitudinal analyses of this growing cohort will allow to value treatment strategies and their outcome in the evolving treatment landscape.

Keywords

- haemophilia
- previously untreated patients
- PUPs
- Inhibitors
- Cohort

Zusammenfassung

Ziele Der Therapiebeginn bei neu diagnostizierten Patienten mit Hämophilie stellt eine Herausforderung dar. Der beste Zeitpunkt, das optimale Therapieregime und die

received
November 28, 2021
accepted after revision
August 22, 2022

DOI https://doi.org/10.1055/s-0042-1757552.
ISSN 0720-9355.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

verwendeten Medikamente waren und sind Gegenstand intensiver Diskussionen. Die Einführung neuer Therapieformen hat die Diskussion weiter verstärkt.

Design Die *German Paediatric Haemophilia Research Database* (GEPHARD) rekrutiert Kinder und Jugendliche bis 18 Jahre mit einer ab dem 01. Januar 2017 neu diagnostizierten Hämophilie A oder B und einer Restaktivität unter 25 IU/dL. Es werden Daten zu Diagnose, Therapie und Outcome erfasst. Im Juni 2021 wurde eine Querschnittsanalyse durchgeführt.

Ergebnisse Daten von 249 Patienten aus 22 Einrichtungen konnten in einer Querschnittstudie analysiert werden. Davon haben 203 Personen eine Hämophilie A (PwHA) und 46 eine Hämophilie B (PwHB). Der Altersmedian bei Diagnosestellung war für jeweils für die schwere Form bei PwHA 6 und bei PwHB 2 Monate, bei Auswertung jeweils 33 und 35 Monate. 117 PwHA mit schwerer Form erhielten zum Zeitpunkt der Analyse eine Therapie, mit plasmatischen (n = 43), rekombinanten (n = 23), halbwertzeitverlängerten, rekombinanten Faktorpräparaten (n = 33) und "Nicht-Faktor"-Präparaten (n = 18). Patienten mit schwerer HB nutzten plasmatische (n = 3), klassische rekombinante (n = 8) oder halbwertzeitverlängerte Präparate (n = 14). Inhibitoren wurden zum Zeitpunkt der Analyse bei 16 PwHA und 1 PwHB gemeldet.

Zusammenfassung GEPHARD konnte erfolgreich als nationale Kohortenstudie neu diagnostizierter, bislang nicht behandelter Patienten mit Hämophilie etabliert werden. In der aktuellen Querschnittsanalyse konnten Daten zu aktuellen Therapieformen ausgewertet werden. Zukünftige, longitudinale Analysen der Kohorte werden weitere Daten zu Behandlungsstrategien, insbesondere auch zum Therapierfolg unter den sich wandelnden Therapieformen liefern.

Introduction

The treatment of patients with haemophilia A (PwHA) or B (PwHB) is evolving rapidly. Novel treatment options including modified clotting factor VIII (FVIII) or factor IX (FIX) molecules and non-replacement therapy together with long established ones offer a wide range of possibilities.[1] As for any novel therapies, there is limited data on safety and efficacy. Real world data on novel treatments are urgently needed in paediatric patients, especially in the very young, previously untreated ones, as these patient groups are not sufficiently represented in preceding clinical trials. Many open questions remain on the optimal treatment for increasing efficacy and reducing inhibitor development.

Several concepts for reduction of inhibitor development including an early, low dose prophylaxis[2,3] have been discussed and studied by trying to avoid environmental risk factors, however these results could not be replicated in a prospective clinical trial.[4] Nevertheless, this concept is widely used in German centres. Registries deliver real world evidence, often have larger patient numbers and allow the collection of high-quality data to better understand and define an optimal – safe and efficacious – early haemophilia treatment.[5]

Data on treatment in previously untreated patients (PUPs) with haemophilia A or B are mainly based on studies with small numbers. Further, the randomised SIPPET trial compared the inhibitor incidence in PwHA treated with recombinant vs plasma-derived FVIII concentrates and indicated a lower inhibitor risk when children were treated with plasma-derived products, however this did not reach statistical significance for high titre inhibitors.[6] Additionally, data from registries and cohorts are available and report partially discordant data. These include international as well as national registries. In Europe, data for PwHA or PwHB are available from Pednet and national cohorts including these in the UK as well as in France.[7–11] The German Haemophilia Registry (DHR) based at the Paul-Ehrlich-Institute focused on legally requested documentation in the past.[12] Almost 30 years ago, a prospective PUP study was initiated among GTH centres. An interim analysis on inhibitor incidence in PwHA conducted in 2002 showed no significant differences for inhibitor development in PwHA treated with plasma-derived or recombinant products available at that time.[13] There are no data available on treatment of PUPs in Germany in the recent years especially in the light of a changing treatment landscape. Thus, the German Paediatric Haemophilia Research data base – GEPHARD – was established by the Standing Committees Paediatrics and Haemophilia of the German Swiss Austrian Society for Thrombosis and Haemostasis Research – GTH to collect data on PUPs in Germany. GEPHARD has been prospectively collecting data since 2017. GEPHARD is designed to allow the exchange of data with other cohorts and will add to the understanding and improvement of treatments of PUPs with haemophilia A and B.

Further to the introduction of GEPHARD, a cross-sectional analysis was performed and is presented based on questionnaires send to participating centres to analyse a larger number of patients and their current treatment in Germany in this young patient cohort at the time of the analysis. Thus, in this manuscript a) details on the GEPHARD study protocol and b) the results of a cross-sectional analysis among GEPHARD participants are presented.

Patients and Methods

Study Design and Population

GEPHARD is a national, multicentre, observational cohort study. Children and adolescents with previously undiagnosed and untreated haemophilia A or B defined as residual factor activity <25 IU/dL and diagnosed after January 1st, 2017 are included in GEPHARD. This cut-off for inclusion was chosen to avoid a reporting bias as many patients with factor levels >25% are diagnosed as adults and to be comparable to existing cohorts, ie. the Pednet cohort. The study is open to any PwH followed at any treatment unit in Germany after IRB approval. Central approval was obtained in Munich (Az 572-16) and Frankfurt (Az 20-540). In addition, local approval was obtained for each documenting centre. Eligible patients can be registered anonymously to better understand the percentage of children finally included for the longitudinal documentation into the registry. After informed consent data are documented into the GEPHARD database using the electronical interface and database structure of the Pednet[7] registry, with separate data files for each cohort. Patients in clinical trials may also be registered and data can be entered after approval of the respective sponsor at the end of the trial. In total, 39 German centres have registered patients in GEPHARD. The study has been registered at the Registry of Patient Registries (RoPR-ID: 11758), at clinicaltrials.gov (NCT02912143) and at the German Clinical Trials Registry (DRKS-ID: 00011101). The study is led by two chairs and a steering committee with representatives from the two committees of the GTH and from the study centres. The study coordination is located at the University Hospital Frankfurt, Goethe University, Department of Paediatrics and Adolescent Medicine.

Further information and contact details are provided on www.gephard.de.

The current report summarizes the results of a cross-sectional analysis, which was based on a questionnaire send to 39 participating centres that had registered at least one patient into GEPHARD. The data set contained information on sex, date of diagnosis, month and year of birth, type of haemophilia including severity and residual factor activity, current type of treatment (prophylaxis, on demand, immune tolerance induction), current factor concentrate or NRT and current inhibitor status.

Documented Parameters in GEPHARD

The initial, anonymous registration includes the date of diagnosis of haemophilia A or B, severity, residual factor activity and age. After inclusion in the study, participants receive a centre specific patient identification number. At baseline characteristics are documented including diagnosis, date of and age at diagnosis, reason for diagnosis, residual factor activity, causative factor 8 or 9 gene mutation, family history of haemophilia and inhibitors and mode of delivery. Detailed data on the first 100 exposure days (ED) are captured including any treatment, reason for treatment, type and location of any bleeds, diagnostic confirmation of bleeds, factor concentrate or non-replacement therapy given, dose and results of inhibitor testing. Type of venous access is also documented. After 100 EDs the participants are documented at least with an annual follow up for participants with a severe or moderate haemophilia as defined by residual factor level and at least every second year for those with a mild haemophilia. Any surgery is documented. In case of inhibitor development any treatment including immune tolerance induction, bypass therapies or NRTs is documented. Moreover, physical activity, joint scores (clinical, ultrasound, x-ray, MRI) and quality of life are documented.

The database is hosted at the Julius Centre of the University Medical Centre Utrecht, the Netherlands. Study centres can directly document into the database individually or are offered a "flying study nurse", who documents on behalf of the centres.

Inhibitor Testing

For all participants in the GEPHARD study, local lab results are documented. A confirmatory testing of antibodies to FVIII or FIX and inhibitors is offered centrally according to clinical practise. Samples are analysed for inhibitors by the Nijmegen modified Bethesda Assay and antibodies against FVIII or FIX are determined including a characterization of the antibody response including epitopes on FVIII or FIX and IgG subclasses.

Satellite Studies

The GEPHARD study group encourages any satellite studies.

Partners

The GEPHARD study was initiated by the Standing Committees Paediatrics and Haemophilia of the Swiss, Austrian and German Society for Thrombosis and Haemostasis Research (GTH e.V.). GEPHARD is closely working together with its partners, the German Haemophilia Registry (DHR),[12] Pednet,[7] the Competence Network Haemorrhagic Diathesis East, the professional organisation of German haemostasis specialists (BDDH e.V.) and the patient organisations DHG e.V. (German Haemophilia Society) and IGH e.V. (Interest Group Haemophilia). GEPHARD receives funding from the pharmaceutical industry (see acknowledgements). All funding companies receive regular reports on the study progress and have no influence on the conduct of the study, the analysis and publication of the data.

Results

Implementation of GEPHARD

GEPHARD was implemented with all regulatory, legal and administrative requirements and the registration and documentation of participants has been started. A study office

with a study coordinator was established. Meeting all requirements and setting up contracts with partners was unexpectedly a big hurdle for a study driven by a study group not registered as a legal entity. The necessary legal bodies were established, IRB approval and contracts with sponsors and centres were placed. Centres are participating actively in GEPHARD and driving the study.

Patients Registered in GEPHARD

From January 2017 to June 30th, 2021 a total of 306 patients from 39 centres were registered in GEPHARD anonymously. Individual centres registered 5 patients (median, range: 1-39). Out of these, 262 (86%) were diagnosed with haemophilia A and 44 (14%) with haemophilia B. PwHA were affected by a severe (n = 156, 59.5%) moderate (n = 32, 12.2%) or mild haemophilia (n = 74, 28,3%). PwHB were affected by a severe (n = 26, 59%), moderate (n = 7, 16%) or mild (n = 11, 25%) haemophilia. Registration was similar during recent years with 58, 69, 64 and 56 patients registered in the years 2017, 2018, 2019 and 2020, respectively. In the first six months of 2021 59 newly diagnosed patients were reported. Due to the pandemic situation the longitudinal documentation was severely hampered. Nevertheless, until June 30th 2021, a total of 59 patients were documented longitudinally. Out of these, 38 reported a severe haemophilia A and 4 a severe haemophilia B. For PwHA, 25 and 23 had a documented follow up of at least 20 or 50 EDs, respectively. For PwHB, three had more than 50 EDs documented.

Cross-sectional Analysis

A cross-sectional analysis presented in this manuscript was performed in June 2021. A total of 306 questionnaires were send to 39 participating centres that have registered patients in GEPHARD. 249 questionnaires (81.4%) from 22 centres were returned and analysed. Individual centres registered 9 patients (median, range: 2-39).

Diagnosis and Severity of Haemophilia

Out of 249 analysed PwH, 203 (81.5%) were diagnosed with haemophilia A and 46 (18,5%) with haemophilia B. PwHA were suffering from severe (n = 122, 60.1%), moderate (n = 24, 11.8%) or mild haemophilia (n = 57, 28.1%). For PwHB, 25 (54.3%), 8 (17.4%) and 13 (28.3%) were suffering from a severe, moderate or mild haemophilia, respectively. Only patients up to a residual factor level of 25 IU/dL were eligible. As expected, the age at diagnosis was associated with the severity of haemophilia. For PwHA the median age at diagnosis was 6, 3 and 16 months for the severe, moderate and mild form of the condition, respectively (►Figure 1 a). For PwHB, the median age at diagnosis was 2, 13 and 40.5 months for the severe, moderate and mild form of the condition, respectively (►Figure 1 b).

Treatment Regimen

For 118 out of 122 patients with severe haemophilia A treatment related data were reported. Most patients (n = 104, 88.1%) received a prophylactic treatment at the time of the cross-sectional analysis and 14 (11.9%) patients

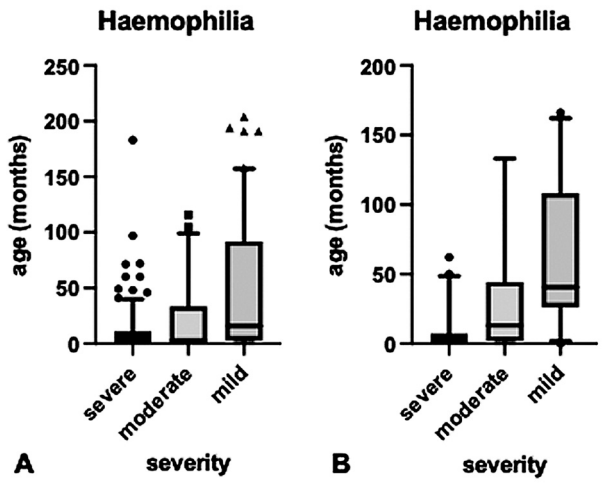

Fig. 1 Age at diagnosis. The age of diagnosis in months of PUPs (n = 249) diagnosed in 2017-2021 is shown according to the severity of haemophilia A (a) or B (b).

were treated on demand. The minority of patients with moderate haemophilia (n = 24) received a prophylactic treatment (n = 5, 20.8%) and the remaining 19 (79.2%) were treated on demand. For 54 patients with mild haemophilia A and a full data set available, 4 (7.4%) received a prophylactic treatment and 50 (92.6%) an on demand treatment. At the time of the cross-sectional analysis, PwHA were 38 months old (median, range: 1.0-256.0), including PwHA with a severe, moderate or mild haemophilia A 33 (1.0-206.0), 36 (8.0-140.0) and 47 (3.0-256.0) months in median (range), respectively.

For 45 out of 46 patients with haemophilia B treatment related data were reported. 23 (92%) out of 25 patients with severe haemophilia were treated prophylactically at the time of the cross-sectional analysis, 2 (8%) were treated on demand. 3 (37.5%) out of 8 patients with moderate haemophilia B and none out of 12 patients with mild haemophilia B were treated prophylactically. At the time of the cross-sectional analysis, PwHB were 40.5 months old (median, range: 0.0-169.0), including PwHB with a severe, moderate or mild haemophilia B 35 (4.0-82.0), 48.5 (1.0-149.0) and 67.0 (0.0-169.0) months in median (range), respectively.

Choice of Concentrate and Prophylactic Agent

Haemophilia A

Data from 196 PwHA of all severities were available. Patients were treated with either plasma-derived FVIII concentrates (n = 73, 37.2%), recombinant FVIII concentrates (n = 42, 21.4%), with a recombinant FVIII concentrate with an extended half-life (n = 45, 23%) or with NRT (n = 19, 9.7%). The remaining patients (n = 17, 8.7%) had not received any treatment yet. For 118 patients with severe haemophilia A, plasma-derived concentrates were used in 43 (36.4%) patients, recombinant FVIII concentrates in 23 (19.5%) patients, recombinant FVIII concentrates with an extended half-life in 33 (28%) patients and 18 (15.3%) patients received

Fig. 2 Choice of concentrates in severe haemophilia A and B. The use of FVIII or FIX concentrates or non-replacement therapy (NRT) is shown in percentage for PwHA (n = 117) (a) or PwHB (n = 25) (b) receiving treatment at the time of the cross-sectional analysis.

NRT (►**Figure 2 a**). Patients with a moderate haemophilia A (n = 24) received plasma-derived (n = 10, 41.7%), recombinant FVIII (n = 10, 41.7%), recombinant FVIII with extended half-life (n = 2, 8.3%) or non-replacement therapy (n = 1, 4.2%). One patient each had not received any medication yet. Further, patients with a mild haemophilia (n = 54) received plasma-derived FVIII (n = 20, 37%), recombinant FVIII (n = 9, 16.7%) or recombinant FVIII with an extended half-life (n = 10, 18.5%). The remaining 15 (27.8%) patients had not yet received treatment. Administered FVIII concentrates included seven different brands of plasma-derived concentrates, seven different recombinant concentrates, one concentrate with an extended half-life and one NRT.

►**Figure 3** shows the treatment at the time of the cross-sectional analysis in patients with severe haemophilia A without current inhibitor according to the year of diagnosis. Whereas the majority of patients diagnosed in 2017 received recombinant FVIII concentrates, the use of recombinant concentrates was less in patients diagnosed in 2018 to 2021. In contrast, the opposite was seen for plasma-derived concentrates: whereas at the time of the cross-sectional analysis 7% of patients diagnosed 2017 received plasma-derived concentrates, the proportion was 60% in patients diagnosed in 2021. The current use of a recombinant extended half-life concentrate was between 21 and 35% for the different years of diagnosis. The current use of NRT was 7% in patients diagnosed in 2017, 6% in 2018, 23% in 2019, 13% in 2020 and 10% in 2021.

Haemophilia B

In total, data for 45 patients diagnosed with haemophilia B were available for analysis. 10 (22.2%) patients received plasma-derived FIX concentrates, 13 (28.9%) recombinant concentrates and 19 (42.2%) recombinant concentrates with extended half-life. The remaining 3 (6.7%) patients have not been treated yet. Out of patients with severe haemophilia B (n = 25), 3 (12%) received a plasma-derived concentrate, 8 (32%) a recombinant concentrate and 14 (56%) a concentrate with an extended half-life. Patients with a moderate haemophilia (n = 8) received recombinant (n = 2, 25%) or an extended half-life concentrate (n = 4, 50%). 2 (25%) patients have not received any treatment yet. Patients with a mild haemophilia (n = 12) received a plasma-derived concentrate (n = 5, 41.7%), a recombinant concentrate (n = 5, 41.7%) or a concentrate with an extended half-life (n = 1, 8.3%). One patient has not received any medication yet.

Administered FIX concentrates included three different brands of plasma-derived concentrates, two different recombinant concentrates and two concentrates with an extended half-life. In patients with severe haemophilia B the percentage of current use of different concentrates was similar for the different years of diagnosis.

Current Inhibitors to FVIII or FIX

17 (8.7%) out of 196 PwHA A had a positive inhibitor to FVIII at the time of the cross-sectional analysis, 16 (13.6%) out of 118 with severe haemophilia A and 1 (1.9%) out of 54 with

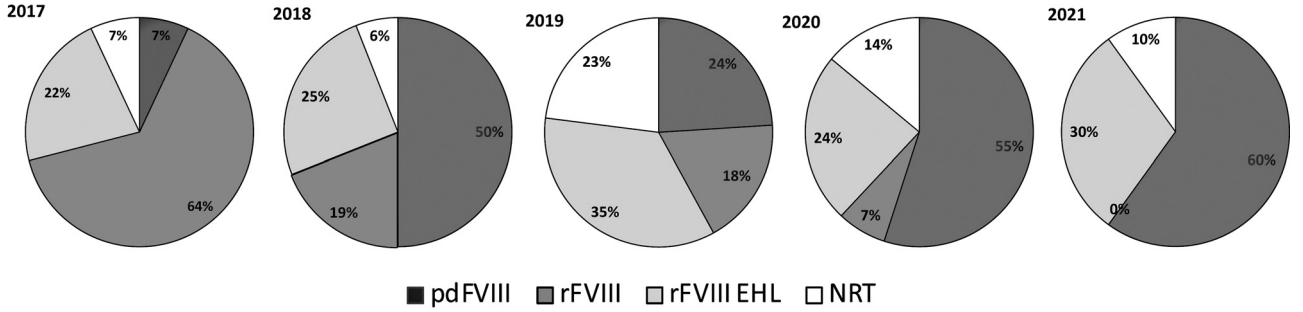

Fig. 3 Current concentrate use according to year of diagnosis. The FVIII or FIX concentrates or non-replacement therapy (NRT) used at the time of this cross-sectional analysis (June 2021) are shown in percentages according to the year of diagnosis.

mild haemophilia A. For 13 patients, information on high- or low-titre inhibitors were available: 9 (69.2%) inhibitor titres were defined as high-titre and 4 (30.8%) as low-titre at the time of the analysis. 11 patients were receiving an immune tolerance induction therapy. The protocols used were not assessed in the cross-sectional analysis. 9 (52.9%) patients received NRT. All patients except for one patient were receiving a FVIII concentrate, 8 as the only treatment and 8 together with NRT. The remaining patient received NRT and activated factor VII. The FVIII concentrates include plasma-derived (n = 2), recombinant (n = 6) ones or a concentrate with extended half-life (n = 8).

For one (4%) out of 25 patients with severe haemophilia B a high-titre inhibitor was reported. The patient was treated with an extended half-life FIX concentrate and activated factor VII.

Discussion

GEPHARD has been established as the national German cohort study for newly diagnosed and untreated patient with haemophilia A or B with a residual factor activity <25 IU/dL irrespective of their treatment regimen. This cut-off was chosen to be comparable with other cohorts (i.e. PedNet) and reflects the Paediatric nature of this cohort as many PwH with factor levels >25 IU/dl are diagnosed during adulthood. GEPHARD is a project of the German members of the Standing Committees Paediatrics and Haemophilia of the GTH and has received a tremendous support from German paediatric haemophilia treatment centres and the research community. This might explain, why the expected number of 40 PUPs per year was outnumbered with a registration of 56 to 69 patients per year in GEPHARD. To our knowledge, this cohort represents the largest group of previously untreated PwH in Germany. While the design of an initial anonymous registration of eligible patients allows for an unselected group of all patients, there might be a bias that not all these patients later consent to further documentation. Also, some patients may be missing, because not all treatment centres in Germany are reporting to GEPHARD. The longitudinal evaluation of this cohort will allow insight into the clinical practise of haemophilia treatment, its development over time and its outcome in Germany. Given the current pandemic situation, the longitudinal documentation progressed slowly. Therefore, a cross-sectional study was performed using a questionnaire to gather data on a significant number of PwH. Out of 309 PwH anonymously registered but not yet longitudinally documented in GEPHARD, data on 249 PwH was collected by questionnaires in the current cross-sectional analysis. Due to its nature, the cross-sectional analysis does not provide data on the evolution of the individual treatment, on inhibitor rate or risk factors for inhibitor development. Nevertheless, this first analysis from the GEPHARD centres gives an overview on the diagnosis and treatment landscape in the largest cohort of paediatric PwH in Germany.

As expected, the age of diagnosis inversely correlated with the severity of haemophilia. At the time of the cross-sectional analysis different plasma-derived, recombinant concentrates, recombinant concentrates with extended half-live and NRT were used. Interestingly, a high proportion of PUPs was treated with plasma derived factor concentrates. This proportion of patients treated with plasma-derived products was higher in more recent years of diagnosis. It is expected that most treatments were not changed within the first exposure days (except for patients with inhibitor development) and that these results may reflect the initial treatment in most cases. Treatment changes are not part of the cross-sectional dataset, thus this can only be speculated upon. The choice of treatment may reflect an influence of the SIPPET trial and also from the German Competence Network Haemorrhagic Diathesis East reporting a lower incidence in PUPs treated with plasma derived concentrates (personal communication R. Knöfler, presented at the GTH annual meeting). A further explanation might be a traditionally higher use of plasma-derived concentrates in Germany in PUPs which is also reflected by a higher rate in GEPHARD compared to the Pednet cohort. Whether these patients are switched to recombinant products later, i.e. after the first 50 exposure days, will be answered by the longitudinal collection of data in GEPHARD. Differences have also been observed for the recombinant and extended half-life concentrates and especially for NRT according to year of diagnosis. For the latter, the highest proportion of NRT was seen in PwHA diagnosed in 2019, whereas its use at the time of this analysis was lower again in PwHA diagnosed in more recent years. The reason for this is unknown but may reflect an increasing discussion on data available in this patient group of infants and young children and on the role of tolerance induction in prophylaxis without FVIII exposure. A recently started PUP trial (NCT04431726, www.clinicaltrials.gov) and longitudinal data from GEPHARD and other cohorts will provide these data in the future. A collaboration of various cohorts using longitudinal data will allow to generate these data in a timely fashion and also on efficacy and inhibitor development of recently licensed concentrates including all concentrates with an extended half-life for the treatment of haemophilia A or B. The proportion of PwH with inhibitors appears rather low. Of note, the numbers do not represent an inhibitor incidence as only positive inhibitors at the time of the analysis are reported. Thus, children before or after inhibitor development are missing. These include children after successful ITI or children with negative inhibitor titres still undergoing ITI and children still at high risk for inhibitor development during early exposure days. Exposure days were not collected during the cross-sectional analysis.

Like many other cohorts, GEPHARD uses laboratory data provided by the local centres, However, in GEPHARD a confirmatory inhibitor diagnostic is offered to all participating centres. A central confirmatory immunological and functional antibody and inhibitor detection will allow further comparisons of clinical and laboratory data to allow the determination of biomarkers for inhibitor development and tolerance induction in a large group of children in a real-world situation. Data from a limited number of patients indicate the relevance of the antibody signature for inhibitor development.[14] The need for such data is even higher in the currently evolving treatment landscape with NRT prophylaxis and exposure to FVIII only

during bleeds or surgery. Identification of biomarkers for inhibitor development may be of even greater importance in children receiving FVIII only for bleed treatment.

The GEPHARD study group has shown its strength in gathering data of a large number of PwHA or PwHB spread all over Germany. With increasing longitudinal documentation and with a close collaboration with GEPHARD partners and other registries, GEPHARD will be able to contribute data on safety and efficacy of haemophilia treatment with a large number of PUPs to provide data on novel therapeutic concepts and novel therapeutic agents in a timelier fashion. Further, GEPHARD has and still is facilitating a closer collaboration between the contributing centres.

Contributors:

Study lead:

Christoph Königs, Universitätsklinikum Frankfurt, Frankfurt am Main and Christoph Bidlingmaier, Dr. von Haunersches Kinderspital, München

Contributors to the cross-sectional analysis:

Volker Aumann, Universitätsklinikum Magdeburg, Magdeburg,
Wolfgang Behnisch, Universitätsklinikum Heidelberg, Heidelberg
Martina Bührlen, Klinikum Bremen Mitte Eltern-Kind Zentrum, Bremen
Martin Chada, Universitätsklinikum Erlangen, Erlangen
Eren Demir, Universitätsklinikum Frankfurt, Frankfurt am Main
Susan Halimeh, Gerinnungszentrum Rhein Ruhr, Duisburg
Wolf Hassenpflug, Universitätsklinikum Hamburg-Eppendorf, Hamburg
Sabine Heine, Universität des Saarlandes, Homburg
Christine Heller, Universitätsklinikum Frankfurt, Frankfurt am Main
Susanne Holzhauer, Charité Universitätsmedizin Berlin, Berlin
Linus Holzschuh, Universitätsklinikum Frankfurt, Frankfurt am Main
Silvia Horneff, Universitätsklinikum Bonn, Bonn
Sebastian Hütker, Oberschwabenklinik, KH St. Elisabeth, Ravensburg
Karim Kentouche, Universitätklinikum Jena, Jena
Sorah Kim, Kinderzentrum am Johannisplatz, Leipzig
Robert Klamoth, Vivantes Klinikum im Friedrichshain, Berlin
Ralf Knöfler, Universitätsklinikum Carl Gustav Carus, Dresden
Sonja Kramer, Universitätsklinikum Regensburg, Regensburg
Karin Kurnik, Dr. von Haunersches Kinderspital, München
Johannes Oldenburg, Universitätsklinikum Bonn, Bonn
Martin Olivieri, Dr. von Haunersches Kinderspital, München Sarah Schober, Universitätsklinikum Tübingen, Tübingen
Stephan Schultze-Strasser, Universitätsklinikum Frankfurt, Frankfurt am Main
Mira Türknetz, Universitätsklinikum Frankfurt, Frankfurt am Main
Vera Vaillant, Universitätsklinikum Gießen und Marburg, Gießen
Verena Wiegering, Universitätsklinikum Würzburg, Würzburg
Ivonne Wieland, Medizinische Hochschule Hannover, Hannover
Jakob Zierk, Universitätsklinikum Erlangen, Erlangen

Study commission

Christoph Bidlingmaier, Dr. von Haunersches Kinderspital, München
Martina Bührlen, Klinikum Bremen Mitte Eltern-Kind Zentrum, Bremen
Wolfgang Eberl, Klinikum Braunschweig, Braunschweig
Carmen Escuriola-Ettingshausen, Hämophilie Zentrum Rhein Main GmbH, Mörfelden
Susan Halimeh, Gerinnungszentrum Rhein Ruhr, Duisburg
Wolf Hassenpflug, Universitätsklinikum Hamburg-Eppendorf, Hamburg
Sabine Heine, Universität des Saarlandes, Homburg
Susanne Holzhauer, Charité Universitätsmedizin Berlin, Berlin
Silvia Horneff, Universitätsklinikum Bonn, Bonn
Karim Kentouche, Universitätklinikum Jena, Jena
Robert Klamoth, Vivantes Klinikum im Friedrichshain, Berlin
Ralf Knöfler, Universitätsklinikum Carl Gustav Carus, Dresden
Christoph Königs, Universitätsklinikum Frankfurt, Frankfurt am Main
Karin Kurnik, Dr. von Haunersches Kinderspital, München
Hans-Jürgen Laws, Universitätsklinikum Düsseldorf
Martin Olivieri, Dr. von Haunersches Kinderspital, München
Monika Sparber-Sauer, Klinikum Stuttgart, Olgahospital, Stuttgart
Michael Sigl-Kraetzig, Blaubeuren
Verena Wiegering, Universitätsklinikum Würzburg, Würzburg
Ivonne Wieland, Medizinische Hochschule Hannover, Hannover Cornelia Wermes, HämoZentrum, Hannover
Barbara Zieger, Universitätsklinikum Freiburg, Freiburg

Author Contribution

CK and CB wrote the paper, MT, ED, LH, CK and CB analysed the data. MT, ED, LH and all other contributors contributed and/or documented data.

Funding

This work was supported by unrestricted grants from Bayer, Biotest, CSL Behring, Grifols, Intersero, Novo Nordisk, Pfizer, Sobi , Takeda

Conflict of Interest

Christoph Königs and Christoph Bidlingmaier report All support for the present manuscript from Bayer

Healthcare, Biotest, CSL Behring, Grifols, Intersero, Novo Nordisk, Pfizer, Sobi, and Takeda; Consulting fees from Bayer, Roche/Chugai, Sobi/Sanofi, Takeda, and CSL Behring; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from BFSH, Novo Nordisk, Sobi/Sanofi, and CSL Behring Support for attending meetings and/or travel from Biotest and Sobi; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid from Co-chair Standing Committee Haemophilia of the GTH.

Acknowledgements

The study group is grateful for the incredible support from all centres, the GTH and its committees, partners, financial supporters and the families and patients, who participate in GEPHARD.

References

1 Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. Lancet 2021;397(10274):630–640. Doi: 10.1016/S0140-6736(20)32722-7
2 Auerswald G, Bidlingmaier C, Kurnik K. Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients–long-term follow-up and continuing experience. Haemophilia 2012;18(01):e18–e20. Doi: 10.1111/j.1365-2516.2011.02659.x
3 Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. Haemophilia 2010;16(02):256–262. Doi: 10.1111/j.1365-2516.2009.02122.x
4 Auerswald G, Kurnik K, Aledort LM, et al; EPIC clinical study group. The EPIC study: a lesson to learn. Haemophilia 2015;21 (05):622–628. Doi: 10.1111/hae.12666
5 Keipert C, Jonker CJ, van den Berg HM, Hilger A. Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources. Haemophilia 2018;24(03):420–428. Doi: 10.1111/hae.13421
6 Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med 2016;374(21):2054–2064. Doi: 10.1056/NEJMoa1516437
7 Fischer K, Ljung R, Platokouki H, et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. Haemophilia 2014;20(04):e280–e286. Doi: 10.1111/hae.12448
8 Calvez T, Chambost H, Claeyssens-Donadel S, et al; FranceCoag Network. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood 2014;124(23):3398–3408. Doi: 10.1182/blood-2014-07-586347
9 Collins PW, Palmer BP, Chalmers EA, et al; UK Haemophilia Centre Doctors' Organization. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. Blood 2014;124(23):3389–3397. Doi: 10.1182/blood-2014-07-580498
10 Gouw SC, van der Bom JG, Ljung R, et al; PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013;368(03):231–239. Doi: 10.1056/NEJMoa1208024
11 Male C, Andersson NG, Rafowicz A, et al. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. Haematologica 2021;106(01): 123–129. Doi: 10.3324/haematol.2019.239160
12 Duda H, Hesse J, Haschberger B, Hilger A, Keipert C. The German Hemophilia Registry: Growing with Its Tasks. J Clin Med 2020;9 (11):E3408. Doi: 10.3390/jcm9113408
13 Kreuz W, Ettingshausen CE, Auerswald G, et al. Epidemiology of inhibitors and current treatment strategies. Haematologica Jun 2003;88(06):EREP04
14 Reipert BM, Gangadharan B, Hofbauer CJ, et al. The prospective Hemophilia Inhibitor PUP Study reveals distinct antibody signatures prior to FVIII inhibitor development. Blood Adv 2020;4(22): 5785–5796. Doi: 10.1182/bloodadvances.2020002731