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Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): Study Protocol

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Keywords: Adherence, Haemophilia, Transition, Adolescents, Young adults

TITLE

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ARTICLE SUMMARY

Abstract

Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleedings from early childhood, which may lead to various complications especially in joints. It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major. The transition from adolescence to adulthood in young people with severe haemophilia is a critical period as it is associated with a high risk of lack of adherence to health care, which might have serious consequences on daily activities but also on quality of life.

Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study to assess the impact of transition from adolescence into adulthood, especially on adherence to health care, among young people with severe haemophilia in France. This study in based on a mixed method, with two complementary and consecutive phases, comparing data from a group of adolescents (aged 14-17 years) to those from a group of young adults (aged 20-29 years). The quantitative phase focuses on the determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of adherence to health care (considered as a marker of the success of transition). The qualitative phase focuses on a more deeply assessment of the psychological mechanisms involved in the transition process for few patients. Eligible patients are contacted by the various Haemophilia Treatment Centres participating in the French national registry FranceCoag

Ethics and dissemination: The study was approved by the French Ethics Committee and by the French National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study findings will be disseminated to the scientific and medical community in peer-reviewed journals and presented at scientific meetings. Results will be popularised to be communicated via the French association for people with haemophilia to participants and to the general public.

Trial registration number: NCT02866526

Word count: 300

Keywords

Adherence / Haemophilia / Transition / Adolescents / Young adults

Strengths and limitations of this study

- The comparison of experiences reported by adolescents compared to those reported by young adults will allow to assess the impact of transition especially on adherence to health care among young people with haemophilia (YPWH) through a cross-sectional study.
- The backing of the French national registry FranceCoag will allow to assess the issue of transition in a large population of YPWH.
- The mixed method of this study will bring original and complementary results by combining quantitative and qualitative methods.
- Determinants of adherence to health care considered as a marker of the success of transition will include classic factors (medical, organisational, and socio-demographic), but also more original ones (social, psychosocial and behavioural).
- Results will serve as the basis to propose recommendations and to develop interventions in order to facilitate the transition process in YPWH.

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INTRODUCTION

Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males (annual incidence: 1/5,000 male births).[1] It is characterized by bleedings due to a lack of clotting factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated, repetition of haemarthroses and haematoma results in invalidating motor disability.

It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the disorder's care management have been described by Young,[2] including:

- The adolescence: independence and responsibility for disease management, self-advocacy and disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers to the patient
- The adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic disease and becoming one's own caregiver

The success of the transition from adolescence to adulthood may therefore be crucial in the maintenance of adherence to care.

In the context of chronic diseases, the process of transition may be more complicated, as affected young people have to deal with a supplementary transition, from a paediatric health care system to an adult one.[3, 4] Indeed, a successful transition involves a transfer of responsibilities from parents to patients concerning the management of their health, the acquisition of the knowledge, abilities, and self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as adults.[5-8] Experiencing a difficult transition could be associated with a decrease in the level of adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted barriers or facilitators to successful transition, either associated to the young patients, or to their parents, or to the various actors of the health care system.[11-14] Authors especially underlined psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of trust in caregivers.[15-17]

In the specific context of haemophilia, some studies have been conducted to assess the issue of transition in young people with haemophilia (YPWH).[18] A study comparing quality of life in YPWH in pre-transition period with YPWH in post-transition period showed a lower quality of life and a higher level of distress in YPWH in post-transition period.[19] Some recommendations (involving patients, families, and caregivers) have been proposed to facilitate this process.[20-22] However, despite the setting up of some actions which have been shown to improve the disease specific knowledge,[23, 24] difficulties are still remaining, which may impair the health condition and the quality of life of YPWH.[25, 26] A study on the unmet needs reported by young adults highlighted psychological issues mainly related to independence achievement.[27] At the crucial age at which adolescents are often opposed or want to take their own decisions, maintaining the adherence to clinical follow-up and therapies is an important issue. Studies have shown a decrease in the level of adherence to the prescribed therapeutic regimen during transition (from 90% for the youngest patients (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years;[28] 59% in another study in YPWH (13-25 years)[29]). This lower adherence might have serious consequences, such as haemarthroses which may impair daily activities but also quality of life. Some psychosocial factors of the maintenance of a high adherence have been highlighted, *e.g.* a greater perception of the need for prophylaxis than the concern over taking it, a positive expectancy of its effectiveness, a good social support, and a stronger emotional reaction to having haemophilia.[30]

Even if some literature data exists on the issue of transition and its impact on adherence to health care in the context of haemophilia, some limits may be discussed. The sample size of these studies is generally modest (below or about a hundred of patients).[30-32] An international larger study including 230 YPWH was conducted but all of them were young adults (aged 18-30 years), none were adolescents.[26] Adherence is usually assessed only through adherence to prophylactic treatment, which excludes YPWH under on-demand treatment.[30-32] None of these studies has been carried out in France where the features of the health care system are very specific. An international study showed that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from Haemophilia Treatment Centres and patients perspectives).[28] Thus, the assumption of all disease-related costs by the French social security system might influence the adherence to care. The backing of the French national registry FranceCoag[33] will allow to assess this issue in a large and exhaustive population of YPWH. This registry involves for more than 20 years French Haemophilia Treatment Centres (HTC), and it includes more than 10,000 patients (7,000 people with haemophilia (PWH), with 2,300 with severe haemophilia of all ages). Moreover, even if some psychological data have been related to the adherence to care, they are often analysed as independent factors. Taking into account the interdependence between these factors using adapted methods could bring original results. Finally, a mixed-design study combining quantitative and qualitative methods will allow to address in a global

way the issue of transition among YPWH, *i.e.* focusing not only on its facilitators and barriers but also, on all the specific concerns and difficulties YPWH may experience as they grow into adulthood.

OBJECTIVES

The main objective of this study is to assess the impact of transition from adolescence into adulthood especially on adherence to health care, among young people with severe haemophilia in France.

The operational objectives of this study are:

- to compare the level of adherence in adolescents and in young adults (YA)
- to identify determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of the level of adherence in YPWH,
- to assess specific factors involved in suboptimal level of adherence in the sub-groups of adolescents on one hand and of YA on the other hand,
- to identify groups of patients (clusters) regarding both their level of adherence and their psychosocial characteristics,
- to examine trough a qualitative approach YPWH needs and expectations towards the health care system during the transition process, and to identify some ways to improve their global care.

METHODS/DESIGN

Study design

This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional study, based on a mixed method, with two complementary and consecutive phases:

- The quantitative phase focuses on the determinants of the level of adherence to health care (considered as a marker of the success of transition), and compares data from a group of adolescents to those from a group of YA,
- The qualitative phase focuses on a more deeply assessment of the psychological mechanisms involved in the transition process for few patients selected from the quantitative phase.

Participants

Inclusion criteria

- Patients with severe A or B haemophilia (deficiency <1%)
- Patients affiliated to the French social security system and included in the FranceCoag registry
- Patients followed in one of the 29 participating HTC
- Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)
- Adolescents authorised to participate by their parents or their legal representatives, or YA who give their consent to participate in this study

Non-inclusion criteria

- Vulnerable patients (adults under guardianship, pregnant or nursing women)
- Patients with reading and writing difficulties

Period of the study

The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two months will focus on results valorisation.

Quantitative phase

Main evaluation criterion

The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (an hypothesized marker of the success of transition into adulthood), which will be assessed via the following items:

- number of follow-up visits in agreement with the recommended number over the last two years,

- number of prophylactic treatment injections in agreement with the recommended number over the last three months (if applicable),
- number of haemorrhagic events over the last two years,
- physician-reported adherence to clinical follow-up and to prophylactic treatment (if applicable),
- patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into account all these dichotomized items. This composite quantitative endpoint will in turn be dichotomized to define adherent / non adherent participants (main evaluation criterion).

Secondary evaluation criteria

Each item which is part of the composite endpoint as described hereinabove will be considered in an independent manner as a secondary evaluation criterion.

Explanatory collected data

Medical data

Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage, major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and current treatment.

Organisational data (Haemophilia Treatment Centres-reported)

Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality, mean age of the transition from paediatric care to adult one, consultations dedicated to the transition, common consultations with both paediatric and adult medical teams, specific tools set up to facilitate the transition process (information leaflet, therapeutic patient education).

Socio-demographic and social data

- Gender and age of family members, living situation,
- Socio-professional category, socio-economic status assessed by the Family Affluence Scale),[34]
- Distance to the HTC (in km),
- Membership of French patients association for PWH (AFH),
- Family functioning (structure, organisation, and communication) assessed by the French validated version of the 6-items Family Assessment Device,[35-37]

- Schooling and academic success evaluated by ad-hoc items (schooling type, level of education, academic difficulties),
- Relationships with the health care system assessed using ad-hoc items (satisfaction and expectations towards the health care system, participation in therapeutic patient education programme).

Psychosocial and behavioural data

- Quality of life will be assessed using the validated French version of the SF-12 generic scale.[38] Two sub-scores, mental health and physical health, will be calculated. The SF-12 allows assessing the quality of life of adults as well as adolescents (14+ years).
  - Quality of life of adolescents will also be assessed by the validated French version of the 10-items Kidscreen Index, which explores the following domains: physical well-being, psychological well-being, autonomy and relations with parents and home life, peers and social support, and school environment.[39]
  - Haemophilia-specific quality of life will be assessed in all participants using the validated French short version of the Haemo-Qol questionnaire.[40, 41]
- Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of the French validated version of the Zimbardo time perspective inventory.[42, 43] The PN subscale (9 items) reflects a pessimistic attitude towards the past and the experience and memory of traumatic life events. The F subscale (12 items) reflects an orientation towards future and an attitude of planning and achievement of objectives. To avoid the questionnaire being too long, we will not plan to assess the Past-Positive, Present-Hedonistic, and Present-Fatalistic subscales.
- Coping Strategies will be measured by the validated French version of the Brief-Cope scale[44, 45] which consists of 28 items assessing individuals' use of 14 coping strategies: self-distraction, active coping, denial, drug use, emotional social support seeking, instrumental social support seeking, behavioural disengagement, emotional expression, positive reframing, planning, humour, acceptation, religion, and self-blame.
- Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire (financial independence from the parents, and living, management of health, dealing with administrative tasks, and taking holidays without the parents). The 15-items Noom validated questionnaire[46, 47] assessing attitudinal autonomy, emotional autonomy, and functional autonomy will be proposed to all participants (ad-hoc translation for this study).

Data collection procedure

Main medical data will be extracted from the FranceCoag database, and completed by a short questionnaire filled in by the referent physician from each HTC. Organisational data will be completed by a medical representative from each HTC. Participants' self-reported data will be collected through a standardised booklet including several questionnaires (an adolescent version and a YA version). Survey documents (information sheet, informed consent and booklet) will be sent by post to eligible YPWH. If no response is received within 30 days, a reminder letter will be sent. A second reminder letter and all survey documents along will be sent two months later in case of no response.

Sample size justification

According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the TRANSHEMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach 99%.[48, 49]

Data Management

A specific database will be created using EpiData software, and merged with the FranceCoag database. A process will be used to assign to each participant a unique anonymous number. A data quality control will be performed by a physician to limit data inconsistency.

Analysis

The analysis plan and the final report will be written according to the STROBE recommendations.[50, 51] All analyses will be performed using R software. All tests will be two-sided, and $p<.05$ will define statistical significance.

Analysis populations

The analysis populations will be the adolescents and the YA groups, among whom adherent and non-adherent patients will be identified.

Descriptive analysis

A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and percentages, quantitative variables as means and standard deviations, or as medians and interquartile ranges. Subjective data will be described by their overall scores and their sub-scores.

Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible patients using basic socio-demographic and clinical data, available in the FranceCoag database.

Comparative analysis

Crude analysis

Adherence will first be described by groups (adolescents / YA) using classical indicators. The comparison of adherence between the two groups will be performed using chi-square test (or Fisher test depending on the expected numbers) for the main evaluation criterion and for all qualitative secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality of the distribution) for quantitative secondary evaluation criteria.

Adjusted analysis

In order to identify factors associated with adherence, bivariate and multivariate analyses will be performed. Potential determinants (medical, organisational, socio-demographic and social, psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression models will be used for the main evaluation criterion and for all qualitative secondary evaluation criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each characteristic whose degree of significance will be lower than .20 will be considered for multivariate analyses. A backward selection will be applied to retain only significantly associated characteristics. Multilevel models will be used to take into account organisational factors which are related to the centre. Structural equation modelling will be considered to take into account the collinearity and/or the complex relationships which might exist between explanatory individual characteristics (especially social, psychological and behavioural ones).[52-54]

This analysis will first be performed in the overall population with a forced adjustment on the group (adolescent / YA). It will secondly be performed independently in each of the two groups.

Cluster analysis

In order to bring to light particular profiles of adherent / non adherent in adolescents on one hand, and in YA on the other hand, an exploratory unsupervised classification analysis will be performed.[55, 56] This method which does not require any condition of validity will allow to gather patients with similar profiles in homogeneous clusters.

Qualitative phase

Data collection procedure

Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the quantitative phase will be selected for this phase according to the following characteristics: adherent or not, and under prophylaxis or not. If they agree, they will be contacted to participate in research

interviews conducted by a psychologist, at any place at their convenience (at home, at the HTC…). The interviews will be individual, confidential, semi-structured, and tape-recorded.

The psychologist will start with a general question, then he/she will adopt a non-directive attitude and will allow the participant to spontaneously and freely broach the answers which they consider relevant. Then he/she will summarise the response and introduce more precise questions regarding the topics which will have not been covered spontaneously or sufficiently by the participant. He/she will seek to focus the interview on the participant's personal experiences, subjective perceptions, and expectancies.

Adolescents' interviews

The interview will begin with this general question: "How do you feel about coming into adulthood in a few years?"

After the spontaneous answer, the psychologist will make them talk about the following topics: the meaning they give to becoming a YA; their expectations towards their life (personal and professional) as future YA; their fears towards their entry into adulthood; their plan to care about their health as future YA.

Young adults' interviews

The interview will begin with this general question: "How do you feel about reaching adulthood during the last few years?"

After the spontaneous answer, the psychologist will make them talk about the following topics: the meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their autonomy (especially concerning the management of their health) and the construction of their life (personal and professional); the facilitators and barriers they identified during their transition process.

Then, to go further and broaden these qualitative data, the psychologist will show to these participants a summary of the adolescents' expectations towards adulthood (from the interviews conducted in adolescents, which therefore will be carried out and analysed before those in YA). The psychologist will then ask YA to assess: to what extent these perceptions match with their own expectations when they were adolescents; to assess to what extent these perceptions match with their current lives; and to indicate which issues regarding transition adolescents forget to mention.

Sample size justification

Four profiles will be identified from the two selected characteristics (adherent or not, and under prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will be selected for the qualitative phase (enrolments until information is saturated).

Data management

All interviews will be precisely and entirely transcribed, including the participants' hesitations and self-corrections.

Analysis

The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand, using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the participants' subjective experiences through the analysis they make of (and the meaning they give to) their feelings and states, as well as the specific events they are faced with. It makes possible to highlight sociocognitive processes by which personal experiences are assimilated to individuals' perceptions of both themselves and the world they live in.[57, 58]

IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read the interview several times, annotating, summarising, paraphrasing, and commenting on what is interesting or significant. The second stage will consist in encoding those annotations to a slightly higher level of abstraction by theoretical and scientific elements: the psychologist will underline the themes addressed by the participant. At the third stage, the psychologist will try to connect these themes by grouping them into superordinate clusters while checking that the connections they make match the meaning of the participant's speech. The last stage of the analysis will consist in giving a scientific meaning to the established clusters.

The same method will be used for all participants within each group, with the permanent goal of improving the previously identified clusters. Each time a new element is identified, or each time a theme or a cluster is modified, the psychologist will get back to previously analysed interviews to ensure that the new model accounts for the speech of all participants.

Finally, when all interviews will have been analysed, a summary will be made, by underlining similarities and differences between adolescents and YA regarding transition into adulthood and its consequences on their lives.

Analyst triangulation will be performed,[59, 60] by involving two psychologists in reviewing the findings in order to assess the reliability and validity of the obtained results. This triangulation may also allow to develop a broader and deeper understanding of the results.

DISCUSSION AND LIMITATIONS

Strengths and limitations of the database

As the issues concerning transition into adulthood may intrinsically depend on features of the health care system, we intend to explore the specific perceptions of YPWH in France, whose health care system model is specific. The support of the FranceCoag registry to this study is therefore an important strength. While the exhaustivity of inclusions in this registry might have been an issue for patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not accept to participate in the TRANSHEMO study, the loss of eligible patients was small (only 4% of the eligible YPWH). The comparison of basic socio-demographic and medical data, available in the FranceCoag database, between included patients and non-included eligible patients will allow to discuss the representativeness of the included sample.

Strengths and limitations of the study design

The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a longitudinal study to follow up YPWH during their transition. However, as this process is long,[2] it would have been very time consuming, with a high risk of lost to follow-up. We therefore chose to compare at a unique time the experiences of two groups regarding their status towards transition. If the results of the present cross-sectional study turned out to be singular, they could justify to secondly set a longitudinal study up.

The mixed study design,[61, 62] by combining quantitative and qualitative methods, will bring original results. The first quantitative phase will allow to adjust the second qualitative phase, by the targeted selection of participants (adherent / non adherent participants according to main evaluation criterion) and by bringing results to be discussed with participants. The qualitative phase will then allow to shed light on the results from the quantitative phase by a deeper analysis of participants' experiences. This qualitative phase could also be a starting point for a future longitudinal and quantitative study, by highlighting unexplored processes by the present quantitative phase.

Strengths and limitations of the endpoints

The main objective of the study is to assess the impact of transition from adolescence to adulthood, which we chose to measure by the level of adherence to health care. This choice is debatable, as maintaining a high level of adherence to care probably reflects only a part of the success of the transition process. However, this choice is justified by several arguments: (i) it is necessary to propose an endpoint which applies for both adolescents and YA, in order to be able to assess through a transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of adherence during the transition process may be associated with clinical consequences (serious

bleedings), which may impair physical and psychological quality of life in YPWH, (iii) this endpoint allows to assess more specifically the impact of the supplementary transition experienced by YPWH, a transition from a paediatric health care system to an adult one, and (iv) this endpoint may be accessible for educational actions.

Adherence is a concept which might be defined by the agreement between the behaviour of a patient and the received recommendations or prescriptions.[63] We chose to assess adherence to prophylactic treatment, which is the commonly used evaluation criterion when assessing adherence in haemophilia[29, 30] but which would have been valid only for YPWH under prophylactic treatment. We therefore also chose to assess adherence to clinical follow-up, which is valid for all YPWH (even if the rhythm of visits might be different depending on their personal situation). Moreover, we chose to collect data on adherence through three sources of information: (i) data from the FranceCoag database (follow-up visits, injections of prophylactic treatment, haemorrhagic events), (ii) referent physician-reported data, and (iii) patient-reported data. A composite endpoint combining these items will allow to take into account the complexity of the assessment of adherence, in particular by mixing clinical and objective data with behavioural and subjective adherence-related data.

Strengths and limitations of the determinants

This study will assess more systematically psychosocial determinants of adherence to health care, considered as a marker of the success of transition. Indeed, beyond the likely impacts of medical, organisational, and socio-demographic factors, we expect this success to be moderated by lesser known sociocognitive (time perspective), emotional (coping strategies), and family factors (family functioning).

Time perspective refers to how individuals partition their experiences into distinct temporal categories of past, present and future.[64] Particular temporal frames may be associated with well-being and quality of life.[65] Indeed, focusing on a “past negative” time perspective may result in negative long-term adjustment and post-traumatic stress symptomology.[66] On the contrary, “future” time perspective has been viewed as the more constructive time perspective.[65]

Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally experience repeated stress reactions because the disease questions individuals about their beliefs, identity, priorities, and short-term and long-term goals.[67, 68] The coping strategies individuals implement to deal with these stress reactions have been studied. Studies show that an individual's inability to implement appropriate coping strategies, or the use of strategies targeting only emotional responses (instead of their cognitive antecedents), are responsible for emotional disorders and impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities, standards, and personal goals.[68-72]

Finally, growing into adulthood implies that young people gain autonomy, get independent and endorse the responsibilities falling to adults. This personal empowerment implies that they develop their own personal values and long-term goals (attitudinal autonomy) and implement effective strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy depends on the capacity to maintain confidence in one's own values and goals (emotional autonomy).[46, 73] We assume the development of autonomy (especially emotional autonomy) largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles management, and communication of emotion.[74-77]

ETHICS

Informed written consent will be obtained for all participants prior to recruitment for the study. For adolescents, consent will be obtained from their two parents or legal representatives. All data will be analysed confidentially and anonymously.

The study was designed according to Good Clinical Practices, and all procedures will be in accordance with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de Protection des Personnes Sud Méditerranée V) on 8th November 2016 and by the French National Agency for Medicines and Health Products Safety on 22th September 2016 (reference number ID RCB: 2016-A01034-47). The protocol was registered in ClinicalTrials.gov (NCT02866526).

DISSEMINATION

This study will allow to comprehend what the impact of transition from adolescence to adulthood could be in YPWH in France, which is of particular interest in the global approach whose goal is to take care of all aspects of life in patients with chronic diseases.

This study will also allow to identify determinants of adherence, considered as a marker of a successful transition in YPWH. The assessment of social, psychosocial and behavioural data, will allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The results obtained from the quantitative phase of the study will be enlightened by the analysis of the interviews conducted in the qualitative phase. This analysis will bring supplementary and complementary data which would not have been accessible via the analysis of the questionnaires, especially concerning expectations and fears about health, but also about personal and professional life. Singular results from this qualitative phase could be used to better design a future quantitative study on the issue of transition, by assessing complementary outcomes to those assessed in the present quantitative phase.

Results will allow to propose recommendations and to develop adapted and focused interventions to compensate for YPWH difficulties, and thus optimize the adherence to the proposed follow-up and to the prophylactic treatment, but also facilitate their entry in the adult life.

In order to assess the transferability of the results from the TRANSHEMO study in other contexts of childhood chronic diseases in France, complementary projects could be proposed to assess the issue of transition in young patients with rare and/or serious and/or chronic diseases. This approach would allow to identify which issues are common to these diseases and which ones are specific to a disease, including severe haemophilia. Common and specific actions could then be proposed to facilitate the transition process and support young patients.

Authors' contributions

NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.

The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG, BG, AH, AH, YH, TL, AL, AL, MM, SM, FM, GM, CN, PN, PN, CO, BP-P, BP, AR, AR, DR, PS, AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres contribute to enrol participants, they revised the manuscript and approved the final version.

Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised the manuscript and approved the final version.

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Competing interests

None declared.

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Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): study protocol for a multicentric French national observational cross-sectional study.

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TITLE

Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): study protocol for a multicentric French national observational cross-sectional study.

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ARTICLE SUMMARY

Abstract

Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleeding from early childhood, which may lead to various complications especially in joints. It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major. The transition from adolescence to adulthood in young people with severe haemophilia is a critical period as it is associated with a high risk of lack of adherence to health care, which might have serious consequences on daily activities but also on quality of life.

Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study to assess the differences between adolescents and young adults with severe haemophilia in France through the transition process, especially on adherence to health care. This study in based on a mixed methods design, with two complementary and consecutive phases, comparing data from a group of adolescents (aged 14-17 years) to those from a group of young adults (aged 20-29 years). The quantitative phase focuses on the determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of adherence to health care (considered as a marker of the success of transition). The qualitative phase explores participants' views in more depth to explain and refine the results from the quantitative phase. Eligible patients are contacted by the various Haemophilia Treatment Centres participating in the French national registry FranceCoag.

Ethics and dissemination: The study was approved by the French Ethics Committee and by the French National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study findings will be disseminated to the scientific and medical community in peer-reviewed journals and presented at scientific meetings. Results will be popularised to be communicated via the French association for people with haemophilia to participants and to the general public.

Trial registration number: NCT02866526

Word count: 299

Keywords

Adherence / Haemophilia / Transition / Adolescents / Young adults

Strengths and limitations of this study

- This study will be the largest to assess the issue of transition from adolescence to adulthood among young people with haemophilia (PWH), and the first one in France where the features of the health care system are very specific.
- The cross-sectional design of the study comparing experiences reported by adolescents compared to those reported by young adults is a limitation, as it would have been pertinent to design a longitudinal study to follow up young PWH during their transition; however, as the transition process is long, it would have been very time consuming with a high risk of follow-up.
- This study will be based on an explanatory sequential mixed methods design, which will allow to bring complementary results by collecting and analysing quantitative and then qualitative data in two consecutive phases within one study.
- The main evaluation criterion of the quantitative phase will be the adherence to health care, a hypothesised marker of the success of transition, whose choice is debatable as it is a complex concept to measure and as it probably reflects only a part of the success of transition.
- Potential determinants will be selected according to the SMART theoretical model (Social-ecological model for adolescents and young adults readiness for transition), and will include both pre-existing objective factors and modifiable subjective factors (potential targets of intervention), whose associations with adherence to health care will be hypothesised from the quantitative phase, and more deeply explored and explained thanks to the qualitative phase.

Word count: 248

INTRODUCTION

Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males (annual incidence: 1/5,000 male births).[1] It is characterized by bleeding due to a lack of clotting factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated, repetition of haemarthroses and haematoma results in invalidating motor disability.

It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the disorder's care management have been described by Young,[2] including:

- Adolescence: independence and responsibility for disease management, self-advocacy and disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers to the patient
- Adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic disease and becoming one's own caregiver

The success of the transition from adolescence to adulthood may therefore be crucial in the maintenance of adherence to care.

In the context of chronic diseases, the process of transition may be more complicated, as affected young people have to deal with a supplementary transition, from a paediatric health care system to an adult one.[3–6] Indeed, a successful transition involves a transfer of responsibilities from parents to patients concerning the management of their health, the acquisition of the knowledge, abilities, and self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as adults.[7, 8] Experiencing a difficult transition could be associated with a decrease in the level of adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted barriers or facilitators to successful transition, either associated to the young patients, or to their parents, or to the various actors of the health care system.[11–14] Authors especially underlined psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of trust in caregivers.[13–16] The theoretical social-ecological model of AYA (adolescents and young adults) readiness for transition (SMART),[17] by identifying both pre-existing objective factors (less amenable to intervention, including socio-demographics/culture, access/insurance, health status/risk,

neurocognition/IQ) and inter-related components of patients, parents and providers (potential targets of intervention, including development, knowledge, skills/self-efficacy, beliefs/expectations, goals, relationships and psychosocial functioning), has been proposed as the ideal framework to identify determinants (barriers and facilitators) of transition in the context of serious paediatric illness conditions.[14] Some interventions have been designed to improve the transition of care, and a Cochrane review assessing their effectiveness found that transitional programs might slightly improve transitional readiness (self-management skills and knowledge), but that they led to little or no difference in health status, quality of life or well-being.[18] The identification of barriers and facilitators to successful transition may help to design target interventions in order to improve their overall effectiveness.

In the specific context of haemophilia, some studies have been conducted to assess the issue of transition in young people with haemophilia (PWH).[19] A study comparing quality of life in young PWH in pre-transition period with young PWH in post-transition period showed a lower quality of life and a higher level of distress in young PWH in post-transition period.[20] Some recommendations (involving patients, families, and caregivers) have been proposed to facilitate this process.[21–23] However, despite the setting up of some actions which have been shown to improve the disease specific knowledge,[24, 25] difficulties are still remaining, which may impair the health condition and the quality of life of young PWH.[26, 27] A study on the unmet needs reported by young adults highlighted psychological issues mainly related to independence achievement.[28] At the crucial age at which adolescents are often opposed or want to take their own decisions, maintaining the adherence to clinical follow-up and therapies is an important issue. A study conducted in young PWH (13-25 years) found that 41% of them had no followed prescribed treatment.[29] Studies have shown a decrease in the level of adherence to the prescribed therapeutic regimen during transition. A study based on nurses-reported data found a decreasing level of adherence, from 90% for the youngest patients (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years.[30] Caregiver or self-reported adherence assessment showed similar results, with a lower level of adherence in adults in comparison with paediatric patients (and among these latter, a lower level in adolescents in comparison with children).[31, 32] This lower adherence might have serious consequences, such as haemarthroses which may impair daily activities but also quality of life. A higher number of hemarthrosis was observed in less-adherent to prophylaxis patients aged 12 to 25 years,[33] which was also observed when considering patients of all ages.[32, 34] Some psychosocial factors of the maintenance of a high adherence in young PWH have been highlighted, *e.g.* a greater perception of the need for prophylaxis than the concern over taking it, a positive expectancy of its effectiveness, a good social support, and a stronger emotional reaction to having haemophilia.[35] In the general framework of haemophilia (not focusing on the transition period), a review on determinants of adherence to prophylactic treatment identified both barriers (absence or infrequent

symptoms, increasing age) and motivators (belief in necessity of treatment, good relationship with the health care provider, experience of symptoms).[36] Another review identified five key types of adherence barriers: patient-related factors (including age), condition-related factors, treatment-related factors, health-care system factors, and socioeconomic factors.[37]

Even if some literature data exists on the issue of transition and its impact on adherence to health care in the context of haemophilia, some limits may be discussed. The sample size of these studies is generally modest (below or about a hundred of patients).[35, 38, 39] An international larger study including 230 young PWH was conducted but all of them were young adults (aged 18-30 years), none were adolescents.[27] Adherence is usually assessed only through adherence to prophylactic treatment, which excludes young PWH under on-demand treatment.[35, 38, 39] None of these studies has been carried out in France where the features of the health care system are very specific. An international study showed that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from Haemophilia Treatment Centres and patients perspectives).[30] Thus, the assumption of all disease-related costs by the French social security system might influence the adherence to care. The backing of the French national registry FranceCoag[40] will allow to assess this issue in a large and exhaustive population of young PWH. This registry involves for more than 20 years French Haemophilia Treatment Centres (HTC), and it includes more than 10,000 patients (7,000 people with haemophilia (PWH), with 2,300 with severe haemophilia of all ages). Moreover, even if some psychological data have been related to the adherence to care, they are often analysed as independent factors. Taking into account the interdependence between these factors using adapted methods could bring original results. Finally, an explanatory sequential mixed methods designed study combining quantitative and qualitative methods will allow to address in a global way the issue of transition among young PWH, *i.e.* focusing not only on its facilitators and barriers but also, on all the specific concerns and difficulties young PWH may experience as they grow into adulthood.

OBJECTIVES

The main objective of this study is to assess differences between adolescents and young adults with severe haemophilia in France, through the transition process, especially on adherence to health care.

The operational objectives of this study are:

- to compare the level of adherence in adolescents and in young adults (YA)
- to identify determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of the level of adherence in young PWH,
- to assess specific factors involved in suboptimal level of adherence in the sub-groups of adolescents and YA,
- to identify groups of patients (clusters) regarding both their level of adherence and their psychosocial characteristics,
- to examine through a qualitative approach statistical results which would have been brought to light according to the quantitative objectives, and to identify some ways to improve adherence to health care in young PWH and their global care.

METHODS/DESIGN

Study design

This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional study, based on an explanatory sequential mixed methods design,[41–47] with two complementary and consecutive phases:

- The quantitative phase focuses on the determinants of adherence to health care (considered as a marker of the success of transition), and compares data from a group of adolescents to those from a group of YA, in order to provide a general understanding of the issue of adherence in young PWH,

The qualitative phase explores participants' views in more depth (few patients selected from the quantitative phase) to explain and refine the general understanding from the quantitative phase. Interpretation and discussion of the global results will be done by integrating the results of both phases of the study.

Participants

Inclusion criteria

- Patients with severe A or B haemophilia (deficiency <1%)
- Patients affiliated to the French social security system and included in the FranceCoag registry
- Patients followed in one of the 29 participating HTC
- Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)

- Adolescents authorised to participate by their parents or their legal representatives, or YA who give their consent to participate in this study

Non-inclusion criteria

- Vulnerable patients (adults under guardianship, pregnant or nursing women)

Patients with reading and writing difficulties (as data collection in the quantitative phase is mostly based on participants' self-reported data collected through a booklet)

Period of the study

The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two months will focus on integrating results from both phases, in order to provide a global interpretation and discussion of the results of the study.

Quantitative phase

Main evaluation criterion

The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (a hypothesized marker of the success of transition into adulthood), which will be assessed via the following items:

- number of follow-up visits in agreement with the recommended number over the last two years,
- number of prophylactic treatment injections in agreement with the recommended number over the last three months (if applicable),
- number of haemorrhagic events over the last two years,
- physician-reported adherence to clinical follow-up and to prophylactic treatment (if applicable),
- patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into account all these dichotomized items. This composite quantitative endpoint will in turn be dichotomized to define adherent / non-adherent participants (main evaluation criterion).

Secondary evaluation criteria

Each item which is part of the composite endpoint as described hereinabove will be considered in an independent manner as a secondary evaluation criterion.

Explanatory collected data

Medical data

Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage,

major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and current treatment.

Organisational data (Haemophilia Treatment Centres-reported)

Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality, mean age of the transition from paediatric care to adult one, consultations dedicated to the transition, common consultations with both paediatric and adult medical teams, specific tools set up to facilitate the transition process (information leaflet, therapeutic patient education).

Socio-demographic and social data

- Gender and age of family members, living situation,
- Socio-professional category, socio-economic status assessed by the Family Affluence Scale),[48]
- Distance to the HTC (in km),
- Membership of French patients association for PWH (AFH),
- Family functioning (structure, organisation, and communication) assessed by the French validated version of the 6-items Family Assessment Device,[49–51]
- Schooling and academic success evaluated by ad-hoc items (schooling type, level of education, academic difficulties),
- Relationships with the health care system assessed using ad-hoc items (satisfaction and expectations towards the health care system, participation in therapeutic patient education programme).

Psychosocial and behavioural data

- Quality of life will be assessed using the validated French version of the SF-12 generic scale.[52] Two sub-scores, mental health and physical health, will be calculated. The SF-12 allows assessing the quality of life of adults as well as adolescents (14 + years).
  - Quality of life of adolescents will also be assessed by the validated French version of the 10-items Kidscreen Index, which explores the following domains: physical well-being, psychological well-being, autonomy and relations with parents and home life, peers and social support, and school environment.[53]
  - Haemophilia-specific quality of life will be assessed in all participants using the validated French short version of the Haemo-Qol questionnaire.[54, 55]
- Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of the French validated version of the Zimbardo time perspective inventory.[56, 57] The PN subscale (9 items) reflects a pessimistic attitude towards the past and the experience and memory of traumatic life events. The F subscale (12 items) reflects an orientation towards future and an attitude of

planning and achievement of objectives. To avoid the questionnaire being too long, we will not plan to assess the Past-Positive, Present-Hedonistic, and Present-Fatalistic subscales.

- Coping Strategies will be measured by the validated French version of the Brief-Cope scale[58, 59] which consists of 28 items assessing individuals' use of 14 coping strategies: self-distraction, active coping, denial, drug use, emotional social support seeking, instrumental social support seeking, behavioural disengagement, emotional expression, positive reframing, planning, humour, acceptance, religion, and self-blame.
- Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire (financial independence from the parents, and living, management of health, dealing with administrative tasks, and taking holidays without the parents). The 15-items Noom validated questionnaire[60, 61] assessing attitudinal autonomy, emotional autonomy, and functional autonomy will be proposed to all participants (ad-hoc translation for this study).

Data collection procedure

Main medical data will be extracted from the FranceCoag database, and completed by a short questionnaire filled in by the referent physician from each HTC. Organisational data will be completed by a medical representative from each HTC. Eligible participants will be identified and approached by the HTC team by which they are followed (approach either during a medical consultation, or by phone call, or by a personalised mail sent at their home). Survey documents (information sheet, informed consent form, booklet, and prepaid envelope) will then be sent by post to eligible young PWH. Participants' self-reported data will be collected through a standardised booklet including several questionnaires (an adolescent version and a YA version). Consent will be collected through the signature of the informed consent form by the parents or the legal representatives for adolescents, and by the signature of the YA directly for YA. Completed questionnaires as well as signed informed consent forms will be sent back by the participants via the supplied prepaid envelope. If no response is received within 30 days, a reminder letter will be sent. A second reminder letter and all survey documents along will be sent two months later in case of no response.

Sample size justification

According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the TRANSHEMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach 99%.[62, 63]

Data Management

A specific database will be created using EpiData software, and merged with the FranceCoag database. A process will be used to assign to each participant a unique anonymous number. A data quality control will be performed by a physician to limit data inconsistency.

Analysis

The analysis plan and the final report will be written according to the STROBE recommendations.[64, 65] All analyses will be performed using R software. All tests will be two-sided, and $p<.05$ will define statistical significance.

Analysis populations

The analysis populations will be the adolescents and the YA groups, among whom adherent and non-adherent patients will be identified.

Descriptive analysis

A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and percentages, quantitative variables as means and standard deviations, or as medians and interquartile ranges. Subjective data will be described by their overall scores and their sub-scores.

Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible patients using basic socio-demographic and clinical data, available in the FranceCoag database.

Comparative analysis

Crude analysis

Adherence will first be described by groups (adolescents / YA) using classical indicators. The comparison of adherence between the two groups will be performed using chi-square test (or Fisher test depending on the expected numbers) for the main evaluation criterion and for all qualitative secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality of the distribution) for quantitative secondary evaluation criteria.

Adjusted analysis

In order to identify factors associated with adherence, bivariate and multivariate analyses will be performed. Potential determinants (medical, organisational, socio-demographic and social, psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression models will be used for the main evaluation criterion and for all qualitative secondary evaluation criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each characteristic whose degree of significance will be lower than .20 will be considered for multivariate analyses. A backward selection will be applied to retain only significantly associated characteristics.

Multilevel models will be used to take into account organisational factors which are related to the centre. Structural equation modelling will be considered to take into account the collinearity and/or the complex relationships which might exist between explanatory individual characteristics (especially social, psychological and behavioural ones).[66–68]

This analysis will first be performed in the overall population with a forced adjustment on the group (adolescent / YA). It will secondly be performed independently in each of the two groups.

Cluster analysis

In order to bring to light particular profiles of adherent / non-adherent in adolescents and in YA, an exploratory unsupervised classification analysis will be performed.[69, 70] This method which does not require any condition of validity will allow to gather patients with similar profiles in homogeneous clusters.

Qualitative phase

Data collection procedure

Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the quantitative phase will be selected for this phase according to the following characteristics (assessed from the quantitative phase): adherent or not, and under prophylaxis or not. If they agree, they will be contacted to participate in research interviews conducted by a psychologist, at any place at their convenience (at home, at the HTC…). The interviews will be individual, confidential, semi-structured, and tape-recorded. The psychologist will be blind to the responses in the questionnaires of the participant, and to his/her status adherent / non-adherent as defined according to the main evaluation criterion of the quantitative phase.

The psychologist will start with a general question, then he/she will adopt a non-directive attitude and will allow the participant to spontaneously and freely broach the answers which they consider relevant. Then he/she will summarise the response and introduce more precise questions regarding the topics which will have not been covered spontaneously or sufficiently by the participant. He/she will seek to focus the interview on the participant's personal experiences, subjective perceptions, and expectancies, in order to understand if the patient is adherent / non-adherent and the possible determinants of this adherence. The interview guide will be refined from the findings from the quantitative phase, in order to collect more specifically data about potential determinants and adherence to health care brought to light from the quantitative phase.

Adolescents' interviews

The interview will begin with this general question: "How do you feel about coming into adulthood in a few years?"

After the spontaneous answer, the psychologist will encourage them to talk about the following topics: the meaning they give to becoming a YA; their expectations towards their life (personal and professional) as future YA; their plan to care about their health as future YA; their fears towards their entry into adulthood.

Young adults' interviews

The interview will begin with this general question: "How do you feel about reaching adulthood during the last few years?"

After the spontaneous answer, the psychologist will encourage them to talk about the following topics: the meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their autonomy (especially concerning the management of their health) and the construction of their life (personal and professional); the facilitators and barriers they identified during their transition process.

Then, to go further and broaden these qualitative data, the psychologist will show to these participants a summary of the adolescents' expectations towards adulthood (from the interviews conducted in adolescents, which therefore will be carried out and analysed before those in YA). The psychologist will then ask YA to assess: to what extent these perceptions match with their own expectations when they were adolescents; to assess to what extent these perceptions match with their current lives; and to indicate which issues regarding transition adolescents forget to mention.

Sample size justification

Four profiles will be identified from the two selected characteristics (adherent or not, and under prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will be selected for the qualitative phase (enrolments until information is saturated).

Data management

All interviews will be precisely and entirely transcribed, including the participants' hesitations and self-corrections.

Analysis

The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand, using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the participants' subjective experiences through the analysis they make of (and the meaning they give to) their feelings and states, as well as the specific events they are faced with. It makes possible to highlight sociocognitive processes by which personal experiences are assimilated to individuals' perceptions of both themselves and the world they live in.[71, 72]

IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read the interview several times, annotating, summarising, paraphrasing, and commenting on what is

interesting or significant. The second stage will consist in encoding those annotations to a slightly higher level of abstraction by theoretical and scientific elements: the psychologist will underline the themes addressed by the participant. At the third stage, the psychologist will try to connect these themes by grouping them into superordinate clusters while checking that the connections they make match the meaning of the participant's speech. The last stage of the analysis will consist in giving a scientific meaning to the established clusters.

The same method will be used for all participants within each group, with the permanent goal of improving the previously identified clusters. Each time a new element is identified, or each time a theme or a cluster is modified, the psychologist will get back to previously analysed interviews to ensure that the new model accounts for the speech of all participants.

According to the interpretation of each interview, the psychologist will have to determine the status adherent / non-adherent of each participant. Thus, the identified clusters of themes will be put in perspective with the psychologist-determined status towards adherence, in order to propose a model describing the relationships between adherence to health care and its determinants.

Finally, when all interviews will have been analysed, a summary will be made, by underlining similarities and differences between adolescents and YA regarding adherence to health care and its determinants, and transition into adulthood and its consequences on their lives.

Analyst triangulation will be performed,[73, 74] by involving two psychologists in reviewing the findings in order to assess the reliability and validity of the obtained results. This triangulation may also allow to develop a broader and deeper understanding of the results.

Interpretation

Interpretation and discussion of the global results of the study will be done by integrating the results of both phases of the study. From participants who will have been considered consistently according to both quantitative and qualitative phases either as adherent or as non-adherent, hypothesized associations between potential determinants and adherence from the quantitative phase will be therefore confirmed or infirmed thanks to the results of the qualitative phase. Thus, combining the quantitative and qualitative findings will help explain the results of the statistical results, which underscores the elaborating purpose for a mixed-methods sequential explanatory design. [45, 75] Participants who will not have been considered consistently either as adherent or as non-adherent will allow to discuss representations and beliefs about adherence in the context of haemophilia, and the relevance of this outcome to assess the success of transition through quantitative studies.

Patient and public involvement

The development of the research question, study design and outcome measures involved interpretation of literature, professional experience reported through the clinicians, nurses, and psychologists working in the various Haemophilia Treatment Centres participating in the French national registry

FranceCoag, and patients' priorities and experience reported through the French association patients association for PWH (AFH) that is member of the steering committee of the study. Patients will not be directly involved in the recruitment, but the AFH will regularly communicate about the study (internet, newsletters, social networks, magazine…) to inform eligible participants in order to maximise the recruitment. Results will be popularised to be communicated via the AFH to participants and to the general public.

DISCUSSION AND LIMITATIONS

Strengths and limitations of the database

As the issues concerning transition into adulthood may intrinsically depend on features of the health care system, we intend to explore the specific perceptions of young PWH in France, whose health care system model is specific. The support of the FranceCoag registry to this study is therefore an important strength. While the exhaustivity of inclusions in this registry might have been an issue for patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not accept to participate in the TRANSHEMO study, the loss of eligible patients was small (only 4% of the eligible young PWH). The comparison of basic socio-demographic and medical data, available in the FranceCoag database, between included patients and non-included eligible patients will allow to discuss the representativeness of the included sample. Moreover, the implication of clinicians, nurses, psychologists, and clinical research associates in both the clinical follow-up of patients and this study via their participation in the FranceCoag registry will help to maximise the recruitment and limit the risk of dropouts for this study. The French patients association for PWH (AFH), member of the steering committee of the FranceCoag registry, will also regularly communicate about the study (internet, newsletters, social networks, magazine…) to inform eligible participants in order to maximise the recruitment.

Strengths and limitations of the study design

The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a longitudinal study to follow up young PWH during their transition. However, as this process is long,[2] it would have been very time consuming, with a high risk of lost to follow-up. We therefore chose to compare at a unique time the experiences of two groups regarding their status towards transition. If the results of the present cross-sectional study turned out to be singular, they could justify to secondly set a longitudinal study up.

The explanatory sequential mixed methods design, [41–47] by combining quantitative and qualitative methods, will bring original results. The first quantitative phase will allow to adjust the second qualitative phase, by the targeted selection of participants (adherent / non-adherent participants according to main evaluation criterion) and by bringing results to be discussed with participants. The qualitative phase will then allow to shed light on the results from the quantitative phase (based on self-reported questionnaires data) by a deeper analysis of participants' experiences collected through interviews conducted by a psychologist, especially for psychosocial and behavioural factors which will have emerged from the quantitative phase. This qualitative phase could also be a starting point for a future longitudinal and quantitative study, by highlighting unexplored processes by the present quantitative phase. The step of integration and mixing of the results from both phases of the study will

allow to more fully answer the question of adherence to health care through the period of transition to adulthood in the context of severe haemophilia, and to develop a more robust and meaningful picture of this issue. Combining the quantitative and qualitative findings will help on one hand to explain relationships between adherence to health care and its determinants, and on the other hand to discuss representations and beliefs about adherence, a quantitative outcome which was considered as a marker of the success of transition.

Strengths and limitations of the endpoints

The main objective of the study is to assess the potential impact of transition from adolescence to adulthood, which we chose to measure by the level of adherence to health care. This choice is debatable, as maintaining a high level of adherence to care probably reflects only a part of the success of the transition process. However, this choice is justified by several arguments: (i) it is necessary to propose an endpoint which applies for both adolescents and YA, in order to be able to assess through a transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of adherence during the transition process may be associated with clinical consequences (serious bleedings), [32–34] which may impair physical and psychological quality of life in young PWH, (iii) this endpoint allows to assess more specifically the potential impact of the supplementary transition experienced by young PWH, a transition from a paediatric health care system to an adult one, (iv) this endpoint was in the top five of health care transition outcomes identified by a Delphi process with an interdisciplinary group of medical and psychosocial professionals,[76] and (v) this endpoint may be accessible for educational actions. Adherence is a concept which might be defined by the agreement between the behaviour of a patient and the received recommendations or prescriptions.[77] We chose to assess adherence to prophylactic treatment, which is the commonly used evaluation criterion when assessing adherence in haemophilia[29, 35] but which would have been valid only for young PWH under prophylactic treatment. We therefore also chose to assess adherence to clinical follow-up, which is valid for all young PWH (even if the rhythm of visits might be different depending on their personal situation). Moreover, we chose to collect data on adherence through three sources of information: (i) data from the FranceCoag database (follow-up visits, injections of prophylactic treatment, haemorrhagic events), (ii) referent physician-reported data, and (iii) patient-reported data. A composite endpoint combining these items will allow to take into account the complexity of the assessment of adherence, in particular by mixing clinical and objective data with behavioural and subjective adherence-related data. The dichotomisation of this composite endpoint to define adherent and non-adherent young PWH will lead to a loss of variability in the data, but this choice will allow to get more accessible data and results. As the issue of variability is sensitive, each secondary endpoint (i.e., each variable included in the composite endpoint) will be analysed according to its original response format (binary, semi-quantitative, quantitative), independently of each other.

Strengths and limitations of the determinants

In this study, the choice of the determinants to be assessed (determinants of adherence to health care, considered as a marker of the success of transition) was based on literature data in the context of haemophilia,[35–37] and this choice was consistent with the theoretical SMART model.[17] This model proposes both potential barriers and facilitators, but also both pre-existing and modifiable factors, more amenable to intervention, including beliefs/expectations related-factors (time perspective) and psychosocial functioning related-factors (coping strategies and family functioning).

Time perspective refers to how individuals partition their experiences into distinct temporal categories of past, present and future.[78] Particular temporal frames may be associated with well-being and quality of life.[79] Indeed, focusing on a "past negative" time perspective may result in negative long-term adjustment and post-traumatic stress symptomology.[80] On the contrary, "future" time perspective has been viewed as the more constructive time perspective.[79]

Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally experience repeated stress reactions because the disease questions individuals about their beliefs, identity, priorities, and short-term and long-term goals.[81, 82] The coping strategies individuals implement to deal with these stress reactions have been studied. Studies show that an individual's inability to implement appropriate coping strategies, or the use of strategies targeting only emotional responses (instead of their cognitive antecedents), are responsible for emotional disorders and impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities, standards, and personal goals.[82–86]

Finally, growing into adulthood implies that young people gain autonomy, get independent and endorse the responsibilities falling to adults. This personal empowerment implies that they develop their own personal values and long-term goals (attitudinal autonomy) and implement effective strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy depends on the capacity to maintain confidence in one's own values and goals (emotional autonomy).[60, 87] We assume the development of autonomy (especially emotional autonomy) largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles management, and communication of emotion.[49, 88–90]

ETHICS

Informed written consent will be obtained for all participants prior to recruitment for the study. For adolescents, consent will be obtained from their two parents or legal representatives. All data will be analysed confidentially and anonymously.

The study was designed according to Good Clinical Practices, and all procedures will be in accordance with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de Protection des Personnes Sud Méditerranée V) on 8th November 2016 and by the French National Agency for Medicines and Health Products Safety on 22th September 2016 (reference number ID RCB: 2016-A01034-47). The protocol was registered in ClinicalTrials.gov (NCT02866526).

DISSEMINATION

This study will allow to comprehend what the potential impact of transition from adolescence to adulthood could be in young PWH in France, which is of particular interest in the global approach whose goal is to take care of all aspects of life in patients with chronic diseases.

This study will also allow to identify determinants of adherence, considered as a marker of a successful transition in young PWH. The assessment of social, psychosocial and behavioural data, will allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The results obtained from the quantitative phase of the study will be enlightened by the analysis of the interviews conducted in the qualitative phase. This analysis will bring supplementary and complementary data which would not have been accessible via the analysis of the questionnaires, especially concerning expectations and fears about health, but also about personal and professional life. Singular results from this qualitative phase could be used to better design a future quantitative study on the issue of transition, by assessing complementary outcomes to those assessed in the present quantitative phase.

Results will allow to propose recommendations and to develop interventions to compensate for young PWH difficulties, and thus optimize the adherence to the proposed follow-up and to the prophylactic treatment, but also facilitate their entry in the adult life. The effectiveness of such transitional programs could be improved by targeting specific patients at risk of difficulties (especially lack of adherence to health care) through the transition process, or by targeting specific needs expressed by young PWH in the present study.[18]

In order to assess the transferability of the results from the TRANSHEMO study in other contexts of childhood chronic diseases in France, complementary projects could be proposed to assess the issue of transition in young patients with rare and/or serious and/or chronic diseases. This approach would allow to identify which issues are common to these diseases and which ones are specific to a disease,

including severe haemophilia. Common and specific actions could then be proposed to facilitate the transition process and support young patients.

Authors' contributions

NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.

The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG, BG, AH, AH, YH, TL, AL, AL, MM, SM, FM, GM, CN, PN, PN, CO, BP-P, BP, AR, AR, DR, PS, AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres contribute to enrol participants, they revised the manuscript and approved the final version.

Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised the manuscript and approved the final version.

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Competing interests

None declared.

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TITLE

Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSHEMO): study protocol for a multicentric French national observational cross-sectional study.

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ARTICLE SUMMARY

Abstract

Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleeding from early childhood, which may lead to various complications especially in joints. It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major. The transition from adolescence to adulthood in young people with severe haemophilia is a critical period as it is associated with a high risk of lack of adherence to health care, which might have serious consequences on daily activities but also on quality of life.

Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study to assess the differences between adolescents and young adults with severe haemophilia in France through the transition process, especially on adherence to health care. This study in based on a mixed methods design, with two complementary and consecutive phases, comparing data from a group of adolescents (aged 14-17 years) to those from a group of young adults (aged 20-29 years). The quantitative phase focuses on the determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of adherence to health care (considered as a marker of the success of transition). The qualitative phase explores participants' views in more depth to explain and refine the results from the quantitative phase. Eligible patients are contacted by the various Haemophilia Treatment Centres participating in the French national registry FranceCoag.

Ethics and dissemination: The study was approved by the French Ethics Committee and by the French National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study findings will be disseminated to the scientific and medical community in peer-reviewed journals and presented at scientific meetings. Results will be popularised to be communicated via the French association for people with haemophilia to participants and to the general public.

Trial registration number: NCT02866526

Word count: 299

Keywords

Adherence / Haemophilia / Transition / Adolescents / Young adults

Strengths and limitations of this study

- This study will be the largest to assess the issue of transition from adolescence to adulthood among young people with haemophilia (PWH), and the first one in France where the features of the health care system are very specific.
- The cross-sectional design of the study comparing experiences reported by adolescents compared to those reported by young adults is a limitation, as it would have been pertinent to design a longitudinal study to follow up young PWH during their transition; however, as the transition process is long, it would have been very time consuming with a high risk of follow-up.
- This study will be based on an explanatory sequential mixed methods design, which will allow to bring complementary results by collecting and analysing quantitative and then qualitative data in two consecutive phases within one study.
- The main evaluation criterion of the quantitative phase will be the adherence to health care, a hypothesised marker of the success of transition, whose choice is debatable as it is a complex concept to measure and as it probably reflects only a part of the success of transition.
- Potential determinants will be selected according to the SMART theoretical model (Social-ecological model for adolescents and young adults readiness for transition), and will include both pre-existing objective factors and modifiable subjective factors (potential targets of intervention), whose associations with adherence to health care will be hypothesised from the quantitative phase, and more deeply explored and explained thanks to the qualitative phase.

Word count: 248

INTRODUCTION

Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males (annual incidence: 1/5,000 male births).[1] It is characterized by bleeding due to a lack of clotting factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated, repetition of haemarthroses and haematoma results in invalidating motor disability.

It is nowadays possible to avoid these complications thanks to substitutive therapies for which the issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the disorder's care management have been described by Young,[2] including:

- Adolescence: independence and responsibility for disease management, self-advocacy and disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers to the patient
- Adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic disease and becoming one's own caregiver

The success of the transition from adolescence to adulthood may therefore be crucial in the maintenance of adherence to care.

In the context of chronic diseases, the process of transition may be more complicated, as affected young people have to deal with a supplementary transition, from a paediatric health care system to an adult one.[3–6] Indeed, a successful transition involves a transfer of responsibilities from parents to patients concerning the management of their health, the acquisition of the knowledge, abilities, and self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as adults.[7, 8] Experiencing a difficult transition could be associated with a decrease in the level of adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted barriers or facilitators to successful transition, either associated to the young patients, or to their parents, or to the various actors of the health care system.[11–14] Authors especially underlined psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of trust in caregivers.[13–16] The theoretical social-ecological model of AYA (adolescents and young adults) readiness for transition (SMART),[17] by identifying both pre-existing objective factors (less amenable to intervention, including socio-demographics/culture, access/insurance, health status/risk,

neurocognition/IQ) and inter-related components of patients, parents and providers (potential targets of intervention, including development, knowledge, skills/self-efficacy, beliefs/expectations, goals, relationships and psychosocial functioning), has been proposed as the ideal framework to identify determinants (barriers and facilitators) of transition in the context of serious paediatric illness conditions.[14] Some interventions have been designed to improve the transition of care, and a Cochrane review assessing their effectiveness found that transitional programs might slightly improve transitional readiness (self-management skills and knowledge), but that they led to little or no difference in health status, quality of life or well-being.[18] The identification of barriers and facilitators to successful transition may help to design target interventions in order to improve their overall effectiveness.

In the specific context of haemophilia, some studies have been conducted to assess the issue of transition in young people with haemophilia (PWH).[19] A study comparing quality of life in young PWH in pre-transition period with young PWH in post-transition period showed a lower quality of life and a higher level of distress in young PWH in post-transition period.[20] Some recommendations (involving patients, families, and caregivers) have been proposed to facilitate this process.[21–23] However, despite the setting up of some actions which have been shown to improve the disease specific knowledge,[24, 25] difficulties are still remaining, which may impair the health condition and the quality of life of young PWH.[26, 27] A study on the unmet needs reported by young adults highlighted psychological issues mainly related to independence achievement.[28] At the crucial age at which adolescents are often opposed or want to take their own decisions, maintaining the adherence to clinical follow-up and therapies is an important issue. A study conducted in young PWH (13-25 years) found that 41% of them had no followed prescribed treatment.[29] Studies have shown a decrease in the level of adherence to the prescribed therapeutic regimen during transition. A study based on nurses-reported data found a decreasing level of adherence, from 90% for the youngest patients (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years.[30] Caregiver or self-reported adherence assessment showed similar results, with a lower level of adherence in adults in comparison with paediatric patients (and among these latter, a lower level in adolescents in comparison with children).[31, 32] This lower adherence might have serious consequences, such as haemarthroses which may impair daily activities but also quality of life. A higher number of hemarthrosis was observed in less-adherent to prophylaxis patients aged 12 to 25 years,[33] which was also observed when considering patients of all ages.[32, 34] Some psychosocial factors of the maintenance of a high adherence in young PWH have been highlighted, *e.g.* a greater perception of the need for prophylaxis than the concern over taking it, a positive expectancy of its effectiveness, a good social support, and a stronger emotional reaction to having haemophilia.[35] In the general framework of haemophilia (not focusing on the transition period), a review on determinants of adherence to prophylactic treatment identified both barriers (absence or infrequent

symptoms, increasing age) and motivators (belief in necessity of treatment, good relationship with the health care provider, experience of symptoms).[36] Another review identified five key types of adherence barriers: patient-related factors (including age), condition-related factors, treatment-related factors, health-care system factors, and socioeconomic factors.[37]

Even if some literature data exists on the issue of transition and its impact on adherence to health care in the context of haemophilia, some limits may be discussed. The sample size of these studies is generally modest (below or about a hundred of patients).[35, 38, 39] An international larger study including 230 young PWH was conducted but all of them were young adults (aged 18-30 years), none were adolescents.[27] Adherence is usually assessed only through adherence to prophylactic treatment, which excludes young PWH under on-demand treatment.[35, 38, 39] None of these studies has been carried out in France where the features of the health care system are very specific. An international study showed that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from Haemophilia Treatment Centres and patients perspectives).[30] Thus, the assumption of all disease-related costs by the French social security system might influence the adherence to care. The backing of the French national registry FranceCoag[40] will allow to assess this issue in a large and exhaustive population of young PWH. This registry involves for more than 20 years French Haemophilia Treatment Centres (HTC), and it includes more than 10,000 patients (7,000 people with haemophilia (PWH), with 2,300 with severe haemophilia of all ages). Moreover, even if some psychological data have been related to the adherence to care, they are often analysed as independent factors. Taking into account the interdependence between these factors using adapted methods could bring original results. Finally, an explanatory sequential mixed methods designed study combining quantitative and qualitative methods will allow to address in a global way the issue of transition among young PWH, *i.e.* focusing not only on its facilitators and barriers but also, on all the specific concerns and difficulties young PWH may experience as they grow into adulthood.

OBJECTIVES

The main objective of this study is to assess differences between adolescents and young adults with severe haemophilia in France, through the transition process, especially on adherence to health care.

The operational objectives of this study are:

- to compare the level of adherence in adolescents and in young adults (YA)
- to identify determinants (medical, organisational, socio-demographic and social, and psychosocial and behavioural factors) of the level of adherence in young PWH,
- to assess specific factors involved in suboptimal level of adherence in the sub-groups of adolescents and YA,
- to identify groups of patients (clusters) regarding both their level of adherence and their psychosocial characteristics,
- to examine through a qualitative approach statistical results which would have been brought to light according to the quantitative objectives, and to identify some ways to improve adherence to health care in young PWH and their global care.

METHODS/DESIGN

Study design

This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional study, based on an explanatory sequential mixed methods design,[41–47] with two complementary and consecutive phases:

- The quantitative phase focuses on the determinants of adherence to health care (considered as a marker of the success of transition), and compares data from a group of adolescents to those from a group of YA, in order to provide a general understanding of the issue of adherence in young PWH,

The qualitative phase explores participants' views in more depth (few patients selected from the quantitative phase) to explain and refine the general understanding from the quantitative phase. Interpretation and discussion of the global results will be done by integrating the results of both phases of the study.

Participants

Inclusion criteria

- Patients with severe A or B haemophilia (deficiency <1%)
- Patients affiliated to the French social security system and included in the FranceCoag registry
- Patients followed in one of the 29 participating HTC

- Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)
- Adolescents authorised to participate by their parents or their legal representatives, or YA who give their consent to participate in this study

Non-inclusion criteria

- Vulnerable patients (adults under guardianship, pregnant or nursing women)

Patients with reading and writing difficulties (as data collection in the quantitative phase is mostly based on participants' self-reported data collected through a booklet)

Period of the study

The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two months will focus on integrating results from both phases, in order to provide a global interpretation and discussion of the results of the study.

Quantitative phase

Main evaluation criterion

The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (a hypothesized marker of the success of transition into adulthood), which will be assessed via the following items:

- number of follow-up visits in agreement with the recommended number over the last two years,
- number of prophylactic treatment injections in agreement with the recommended number over the last three months (if applicable),
- number of haemorrhagic events over the last two years,
- physician-reported adherence to clinical follow-up and to prophylactic treatment (if applicable),
- patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into account all these dichotomized items. This composite quantitative endpoint will in turn be dichotomized to define adherent / non-adherent participants (main evaluation criterion).

Secondary evaluation criteria

Each item which is part of the composite endpoint as described hereinabove will be considered in an independent manner as a secondary evaluation criterion.

Explanatory collected data

Medical data

Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage, major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and current treatment.

Organisational data (Haemophilia Treatment Centres-reported)

Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality, mean age of the transition from paediatric care to adult one, consultations dedicated to the transition, common consultations with both paediatric and adult medical teams, specific tools set up to facilitate the transition process (information leaflet, therapeutic patient education).

Socio-demographic and social data

- Gender and age of family members, living situation,
- Socio-professional category, socio-economic status assessed by the Family Affluence Scale),[48]
- Distance to the HTC (in km),
- Membership of French patients association for PWH (AFH),
- Family functioning (structure, organisation, and communication) assessed by the French validated version of the 6-items Family Assessment Device,[49–51]
- Schooling and academic success evaluated by ad-hoc items (schooling type, level of education, academic difficulties),
- Relationships with the health care system assessed using ad-hoc items (satisfaction and expectations towards the health care system, participation in therapeutic patient education programme).

Psychosocial and behavioural data

- Quality of life will be assessed using the validated French version of the SF-12 generic scale.[52] Two sub-scores, mental health and physical health, will be calculated. The SF-12 allows assessing the quality of life of adults as well as adolescents (14 + years).
    - Quality of life of adolescents will also be assessed by the validated French version of the 10-items Kidscreen Index, which explores the following domains: physical well-being, psychological well-being, autonomy and relations with parents and home life, peers and social support, and school environment.[53]
    - Haemophilia-specific quality of life will be assessed in all participants using the validated French short version of the Haemo-Qol questionnaire.[54, 55]

- Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of the French validated version of the Zimbardo time perspective inventory.[56, 57] The PN subscale (9 items) reflects a pessimistic attitude towards the past and the experience and memory of traumatic life events. The F subscale (12 items) reflects an orientation towards future and an attitude of planning and achievement of objectives. To avoid the questionnaire being too long, we will not plan to assess the Past-Positive, Present-Hedonistic, and Present-Fatalistic subscales.
- Coping Strategies will be measured by the validated French version of the Brief-Cope scale[58, 59] which consists of 28 items assessing individuals' use of 14 coping strategies: self-distraction, active coping, denial, drug use, emotional social support seeking, instrumental social support seeking, behavioural disengagement, emotional expression, positive reframing, planning, humour, acceptance, religion, and self-blame.
- Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire (financial independence from the parents, and living, management of health, dealing with administrative tasks, and taking holidays without the parents). The 15-items Noom validated questionnaire[60, 61] assessing attitudinal autonomy, emotional autonomy, and functional autonomy will be proposed to all participants (ad-hoc translation for this study).

Data collection procedure

Main medical data will be extracted from the FranceCoag database, and completed by a short questionnaire filled in by the referent physician from each HTC. Organisational data will be completed by a medical representative from each HTC. Eligible participants will be identified and approached by the HTC team by which they are followed (approach either during a medical consultation, or by phone call, or by a personalised mail sent at their home). Survey documents (information sheet, informed consent form, booklet, and prepaid envelope) will then be sent by post to eligible young PWH. Participants' self-reported data will be collected through a standardised booklet including several questionnaires (an adolescent version and a YA version). Consent will be collected through the signature of the informed consent form by the parents or the legal representatives for adolescents, and by the signature of the YA directly for YA. Completed questionnaires as well as signed informed consent forms will be sent back by the participants via the supplied prepaid envelope. If no response is received within 30 days, a reminder letter will be sent. A second reminder letter and all survey documents along will be sent two months later in case of no response.

Sample size justification

According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the TRANSHEMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of

adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach 99%.[62, 63]

Data Management

A specific database will be created using EpiData software, and merged with the FranceCoag database. A process will be used to assign to each participant a unique anonymous number. A data quality control will be performed by a physician to limit data inconsistency.

Analysis

The analysis plan and the final report will be written according to the STROBE recommendations.[64, 65] All analyses will be performed using R software. All tests will be two-sided, and $p<.05$ will define statistical significance.

Analysis populations

The analysis populations will be the adolescents and the YA groups, among whom adherent and non-adherent patients will be identified.

Descriptive analysis

A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and percentages, quantitative variables as means and standard deviations, or as medians and interquartile ranges. Subjective data will be described by their overall scores and their sub-scores.

Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible patients using basic socio-demographic and clinical data, available in the FranceCoag database.

Comparative analysis

Crude analysis

Adherence will first be described by groups (adolescents / YA) using classical indicators. The comparison of adherence between the two groups will be performed using chi-square test (or Fisher test depending on the expected numbers) for the main evaluation criterion and for all qualitative secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality of the distribution) for quantitative secondary evaluation criteria.

Adjusted analysis

In order to identify factors associated with adherence, bivariate and multivariate analyses will be performed. Potential determinants (medical, organisational, socio-demographic and social, psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression

models will be used for the main evaluation criterion and for all qualitative secondary evaluation criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each characteristic whose degree of significance will be lower than .20 will be considered for multivariate analyses. A backward selection will be applied to retain only significantly associated characteristics. Multilevel models will be used to take into account organisational factors which are related to the centre. Structural equation modelling will be considered to take into account the collinearity and/or the complex relationships which might exist between explanatory individual characteristics (especially social, psychological and behavioural ones).[66–68]

This analysis will first be performed in the overall population with a forced adjustment on the group (adolescent / YA). It will secondly be performed independently in each of the two groups.

Cluster analysis

In order to bring to light particular profiles of adherent / non-adherent in adolescents and in YA, an exploratory unsupervised classification analysis will be performed.[69, 70] This method which does not require any condition of validity will allow to gather patients with similar profiles in homogeneous clusters.

Qualitative phase

Data collection procedure

Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the quantitative phase will be selected for this phase according to the following characteristics (assessed from the quantitative phase): adherent or not, and under prophylaxis or not. If they agree, they will be contacted to participate in research interviews conducted by a psychologist, at any place at their convenience (at home, at the HTC…). The interviews will be individual, confidential, semi-structured, and tape-recorded. The psychologist will be blind to the responses in the questionnaires of the participant, and to his/her status adherent / non-adherent as defined according to the main evaluation criterion of the quantitative phase.

The psychologist will start with a general question, then he/she will adopt a non-directive attitude and will allow the participant to spontaneously and freely broach the answers which they consider relevant. Then he/she will summarise the response and introduce more precise questions regarding the topics which will have not been covered spontaneously or sufficiently by the participant. He/she will seek to focus the interview on the participant's personal experiences, subjective perceptions, and expectancies, in order to understand if the patient is adherent / non-adherent and the possible determinants of this adherence. The interview guide will be refined from the findings from the quantitative phase, in order to collect more specifically data about potential determinants and adherence to health care brought to light from the quantitative phase.

Adolescents' interviews

The interview will begin with this general question: "How do you feel about coming into adulthood in a few years?"

After the spontaneous answer, the psychologist will encourage them to talk about the following topics: the meaning they give to becoming a YA; their expectations towards their life (personal and professional) as future YA; their plan to care about their health as future YA; their fears towards their entry into adulthood.

Young adults' interviews

The interview will begin with this general question: "How do you feel about reaching adulthood during the last few years?"

After the spontaneous answer, the psychologist will encourage them to talk about the following topics: the meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their autonomy (especially concerning the management of their health) and the construction of their life (personal and professional); the facilitators and barriers they identified during their transition process.

Then, to go further and broaden these qualitative data, the psychologist will show to these participants a summary of the adolescents' expectations towards adulthood (from the interviews conducted in adolescents, which therefore will be carried out and analysed before those in YA). The psychologist will then ask YA to assess: to what extent these perceptions match with their own expectations when they were adolescents; to assess to what extent these perceptions match with their current lives; and to indicate which issues regarding transition adolescents forget to mention.

Sample size justification

Four profiles will be identified from the two selected characteristics (adherent or not, and under prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will be selected for the qualitative phase (enrolments until information is saturated).

Data Management

All interviews will be precisely and entirely transcribed, including the participants' hesitations and self-corrections.

Analysis

The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand, using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the participants' subjective experiences through the analysis they make of (and the meaning they give to) their feelings and states, as well as the specific events they are faced with. It makes possible to

highlight sociocognitive processes by which personal experiences are assimilated to individuals' perceptions of both themselves and the world they live in.[71, 72]

IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read the interview several times, annotating, summarising, paraphrasing, and commenting on what is interesting or significant. The second stage will consist in encoding those annotations to a slightly higher level of abstraction by theoretical and scientific elements: the psychologist will underline the themes addressed by the participant. At the third stage, the psychologist will try to connect these themes by grouping them into superordinate clusters while checking that the connections they make match the meaning of the participant's speech. The last stage of the analysis will consist in giving a scientific meaning to the established clusters.

The same method will be used for all participants within each group, with the permanent goal of improving the previously identified clusters. Each time a new element is identified, or each time a theme or a cluster is modified, the psychologist will get back to previously analysed interviews to ensure that the new model accounts for the speech of all participants.

According to the interpretation of each interview, the psychologist will have to determine the status adherent / non-adherent of each participant. Thus, the identified clusters of themes will be put in perspective with the psychologist-determined status towards adherence, in order to propose a model describing the relationships between adherence to health care and its determinants.

Finally, when all interviews will have been analysed, a summary will be made, by underlining similarities and differences between adolescents and YA regarding adherence to health care and its determinants, and transition into adulthood and its consequences on their lives.

Analyst triangulation will be performed,[73, 74] by involving two psychologists in reviewing the findings in order to assess the reliability and validity of the obtained results. This triangulation may also allow to develop a broader and deeper understanding of the results.

Interpretation

Interpretation and discussion of the global results of the study will be done by integrating the results of both phases of the study. From participants who will have been considered consistently according to both quantitative and qualitative phases either as adherent or as non-adherent, hypothesized associations between potential determinants and adherence from the quantitative phase will be therefore confirmed or infirmed thanks to the results of the qualitative phase. Thus, combining the quantitative and qualitative findings will help explain the results of the statistical results, which underscores the elaborating purpose for a mixed-methods sequential explanatory design. [45, 75] Participants who will not have been considered consistently either as adherent or as non-adherent will allow to discuss representations and beliefs about adherence in the context of haemophilia, and the relevance of this outcome to assess the success of transition through quantitative studies.

Patient and public involvement

The development of the research question, study design and outcome measures involved interpretation of literature, professional experience reported through the clinicians, nurses, and psychologists working in the various Haemophilia Treatment Centres participating in the French national registry FranceCoag, and patients' priorities and experience reported through the French association patients association for PWH (AFH) that is member of the steering committee of the study. Patients will not be directly involved in the recruitment, but the AFH will regularly communicate about the study (internet, newsletters, social networks, magazine…) to inform eligible participants in order to maximise the recruitment. Results will be popularised to be communicated via the AFH to participants and to the general public.

DISCUSSION AND LIMITATIONS

Strengths and limitations of the database

As the issues concerning transition into adulthood may intrinsically depend on features of the health care system, we intend to explore the specific perceptions of young PWH in France, whose health care system model is specific. The support of the FranceCoag registry to this study is therefore an important strength. While the exhaustivity of inclusions in this registry might have been an issue for patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not accept to participate in the TRANSHEMO study, the loss of eligible patients was small (only 4% of the eligible young PWH). The comparison of basic socio-demographic and medical data, available in the FranceCoag database, between included patients and non-included eligible patients will allow to discuss the representativeness of the included sample. Moreover, the implication of clinicians, nurses, psychologists, and clinical research associates in both the clinical follow-up of patients and this study via their participation in the FranceCoag registry will help to maximise the recruitment and limit the risk of dropouts for this study. The French patients association for PWH (AFH), member of the steering committee of the FranceCoag registry, will also regularly communicate about the study (internet, newsletters, social networks, magazine…) to inform eligible participants in order to maximise the recruitment.

Strengths and limitations of the study design

The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a longitudinal study to follow up young PWH during their transition. However, as this process is long,[2] it would have been very time consuming, with a high risk of lost to follow-up. We therefore chose to compare at a unique time the experiences of two groups regarding their status towards transition. If the results of the present cross-sectional study turned out to be singular, they could justify to secondly set a longitudinal study up.

The explanatory sequential mixed methods design, [41–47] by combining quantitative and qualitative methods, will bring original results. The first quantitative phase will allow to adjust the second qualitative phase, by the targeted selection of participants (adherent / non-adherent participants according to main evaluation criterion) and by bringing results to be discussed with participants. The qualitative phase will then allow to shed light on the results from the quantitative phase (based on self-reported questionnaires data) by a deeper analysis of participants' experiences collected through interviews conducted by a psychologist, especially for psychosocial and behavioural factors which will have emerged from the quantitative phase. This qualitative phase could also be a starting point for a future longitudinal and quantitative study, by highlighting unexplored processes by the present quantitative phase. The step of integration and mixing of the results from both phases of the study will

allow to more fully answer the question of adherence to health care through the period of transition to adulthood in the context of severe haemophilia, and to develop a more robust and meaningful picture of this issue. Combining the quantitative and qualitative findings will help both to explain relationships between adherence to health care and its determinants, and to discuss representations and beliefs about adherence, a quantitative outcome which was considered as a marker of the success of transition.

Strengths and limitations of the endpoints

The main objective of the study is to assess the potential impact of transition from adolescence to adulthood, which we chose to measure by the level of adherence to health care. This choice is debatable, as maintaining a high level of adherence to care probably reflects only a part of the success of the transition process. However, this choice is justified by several arguments: (i) it is necessary to propose an endpoint which applies for both adolescents and YA, in order to be able to assess through a transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of adherence during the transition process may be associated with clinical consequences (serious bleedings), [32–34] which may impair physical and psychological quality of life in young PWH, (iii) this endpoint allows to assess more specifically the potential impact of the supplementary transition experienced by young PWH, a transition from a paediatric health care system to an adult one, (iv) this endpoint was in the top five of health care transition outcomes identified by a Delphi process with an interdisciplinary group of medical and psychosocial professionals,[76] and (v) this endpoint may be accessible for educational actions. Adherence is a concept which might be defined by the agreement between the behaviour of a patient and the received recommendations or prescriptions.[77] We chose to assess adherence to prophylactic treatment, which is the commonly used evaluation criterion when assessing adherence in haemophilia[29, 35] but which would have been valid only for young PWH under prophylactic treatment. We therefore also chose to assess adherence to clinical follow-up, which is valid for all young PWH (even if the rhythm of visits might be different depending on their personal situation). Moreover, we chose to collect data on adherence through three sources of information: (i) data from the FranceCoag database (follow-up visits, injections of prophylactic treatment, haemorrhagic events), (ii) referent physician-reported data, and (iii) patient-reported data. A composite endpoint combining these items will allow to take into account the complexity of the assessment of adherence, in particular by mixing clinical and objective data with behavioural and subjective adherence-related data. The dichotomisation of this composite endpoint to define adherent and non-adherent young PWH will lead to a loss of variability in the data, but this choice will allow to get more accessible data and results. As the issue of variability is sensitive, each secondary endpoint (i.e., each variable included in the composite endpoint) will be analysed according to its original response format (binary, semi-quantitative, quantitative), independently of each other.

Strengths and limitations of the determinants

In this study, the choice of the determinants to be assessed (determinants of adherence to health care, considered as a marker of the success of transition) was based on literature data in the context of haemophilia,[35–37] and this choice was consistent with the theoretical SMART model.[17] This model proposes both potential barriers and facilitators, but also both pre-existing and modifiable factors, more amenable to intervention, including beliefs/expectations related-factors (time perspective) and psychosocial functioning related-factors (coping strategies and family functioning).

Time perspective refers to how individuals partition their experiences into distinct temporal categories of past, present and future.[78] Particular temporal frames may be associated with well-being and quality of life.[79] Indeed, focusing on a "past negative" time perspective may result in negative long-term adjustment and post-traumatic stress symptomology.[80] On the contrary, "future" time perspective has been viewed as the more constructive time perspective.[79]

Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally experience repeated stress reactions because the disease questions individuals about their beliefs, identity, priorities, and short-term and long-term goals.[81, 82] The coping strategies individuals implement to deal with these stress reactions have been studied. Studies show that an individual's inability to implement appropriate coping strategies, or the use of strategies targeting only emotional responses (instead of their cognitive antecedents), are responsible for emotional disorders and impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities, standards, and personal goals.[82–86]

Finally, growing into adulthood implies that young people gain autonomy, get independent and endorse the responsibilities falling to adults. This personal empowerment implies that they develop their own personal values and long-term goals (attitudinal autonomy) and implement effective strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy depends on the capacity to maintain confidence in one's own values and goals (emotional autonomy).[60, 87] We assume the development of autonomy (especially emotional autonomy) largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles management, and communication of emotion.[49, 88–90]

ETHICS

Informed written consent will be obtained for all participants prior to recruitment for the study. For adolescents, consent will be obtained from their two parents or from their legal representatives, in line with the French laws and regulations. All data will be analysed confidentially and anonymously.

The study was designed according to Good Clinical Practices, and all procedures will be in accordance with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de Protection des Personnes Sud Méditerranée V) on 8th November 2016 and by the French National Agency for Medicines and Health Products Safety on 22th September 2016 (reference number ID RCB: 2016-A01034-47). Data collection, recording, and analysis process was approved by the French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés, authorisation number 918045), and this approval was in line with the General Data Protection Regulation principles. The protocol was registered in ClinicalTrials.gov (NCT02866526).

DISSEMINATION

This study will allow to comprehend what the potential impact of transition from adolescence to adulthood could be in young PWH in France, which is of particular interest in the global approach whose goal is to take care of all aspects of life in patients with chronic diseases.

This study will also allow to identify determinants of adherence, considered as a marker of a successful transition in young PWH. The assessment of social, psychosocial and behavioural data, will allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The results obtained from the quantitative phase of the study will be enlightened by the analysis of the interviews conducted in the qualitative phase. This analysis will bring supplementary and complementary data which would not have been accessible via the analysis of the questionnaires, especially concerning expectations and fears about health, but also about personal and professional life. Singular results from this qualitative phase could be used to better design a future quantitative study on the issue of transition, by assessing complementary outcomes to those assessed in the present quantitative phase.

Results will allow to propose recommendations and to develop interventions to compensate for young PWH difficulties, and thus optimize the adherence to the proposed follow-up and to the prophylactic treatment, but also facilitate their entry in the adult life. The effectiveness of such transitional programs could be improved by targeting specific patients at risk of difficulties (especially lack of adherence to health care) through the transition process, or by targeting specific needs expressed by young PWH in the present study.[18]

In order to assess the transferability of the results from the TRANSHEMO study in other contexts of childhood chronic diseases in France, complementary projects could be proposed to assess the issue of transition in young patients with rare and/or serious and/or chronic diseases. This approach would allow to identify which issues are common to these diseases and which ones are specific to a disease, including severe haemophilia. Common and specific actions could then be proposed to facilitate the transition process and support young patients.

Authors' contributions

NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.

The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG, BG, AH, AH, YH, TL, AL, AL, MM, SM, FM, GM, CN, PN, PN, CO, BP-P, BP, AR, AR, DR, PS, AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres contribute to enrol participants, they revised the manuscript and approved the final version.

Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised the manuscript and approved the final version.

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Competing interests

None declared.

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