Great Ormond Street Hospital for Children NHS Foundation Trust

Royal Free London NHS Foundation Trust

UCL

Investigating the long-term outcomes of adult patients who underwent Haematopoietic Stem Cell Transplant for Primary Immunodeficiency during Childhood
(Post HSCT Follow-up)

Background

Haematopoietic stem cell transplantation for Primary Immunodeficiency

Primary Immunodeficiency (PID) is an umbrella term for a group of rare disorders of the immune system (Fischer et al., 1997) with an estimated prevalence of at least 1 in 15-20,000 (Bousfiha et al., 2013). While some PIDs have specific features, including manifestations outside the immune system, an increased susceptibility to infection are their hallmark. Over 300 genes have been identified to cause specific PIDs, with variability in clinical phenotype and severity (Al-Herz et al., 2014). Most PID presenting in childhood are of severe phenotype and associated with life-threatening infections. Haematopoietic stem cell transplantation (HSCT) is the treatment of choice and offers the hope of 'cure' for severe PID in childhood. HSCT for paediatric PID makes up <10% of the total in the UK (NHS Commissioning Board, 2013) and is limited to two super-specialised centres: Great Ormond Street Hospital (GOSH) and the Great North Children's Hospital, Newcastle. An increasing number of children with PID undergo HSCT each year (Passweg, 2013), with approximately 35 procedures performed annually at GOSH. Due to improvements in technology and supportive care, over 80% of patients now survive long-term, creating an expanding cohort of adult survivors of HSCT for PID in the UK.

Medical Outcomes following HSCT

HSCT for PID is a high risk procedure and associated with long-term medical complications, both as a consequence of the underlying PID and as late effects of the transplant procedure (Eapen et al., 2012). Factors known to influence medical outcome include genetic PID diagnosis, donor type, conditioning and engraftment, clinical condition prior to transplant and GVHD (Dvorak & Cowan, 2008; Hassan et al., 2012; Gennery et al., 2010; Gungor et al., 2014; Moratto et al., 2011; Neven, Cavanzann-Calvo & Fischer, 2008; Tewari et al., 2012). In medium-term follow-up studies (around 5 years post HSCT) a number of medical problems have been described, including growth and fertility, hearing, respiratory, gastroenterological and dermatological problems (Honig et al., 2007; Mazzolari et al., 2007; Patel et al., 2008; Seger et al., 2002; Sonici et al., 2009). Analysis of later effects specific to PID is limited but information from HSCT for other conditions indicates that chronic GVHD, organ dysfunction and secondary malignancies are significant contributors to longer term effects, including late mortality up to 15 years post-HSCT (Bhatia et al., 2007).

Psychosocial Outcomes following HSCT

Most of the research investigating outcomes following HSCT for PID has focused on physical outcomes and there has been little assessment of psychosocial measures. Whilst quality of life is referred to (Duell et al., 1997; Dvorak et al., 2013; Patel et al., 2008; Patel et al., 2009; Seger et al., 2002; Soncini et al., 2009; Tewari et al., 2012) specific measures were not used and there was a low threshold for 'good' quality of life (e.g., being alive and/or attending school). Five studies examined psychosocial outcomes and/or quality of life for patients who underwent HSCT for PID (Cole et al., 2013; Nuss & Wilson, 2007; Sanders et al., 2010; Skucek et al., 2011; Titman et al., 2008). Four of these looked at short-term follow-up in children and only three were limited to patients with PID. The results indicated some emotional and social difficulties and a long-term impact on quality of life, with variation according to original diagnosis (Cole et al., 2013; Nuss & Wilson, 2007; Skucek et al., 2011, Titman et al., 2008). The fifth study (Sanders et al., 2010) examined late outcome in adult

survivors of childhood HSCT, but less than 25% of their sample were patients with PID (specific number and diagnoses not provided). The paediatric literature shows that there are outcomes differences between patients transplanted for PID and other diagnoses (Phipps et al., 2008) and between patients with different PIDs (Titman et al., 2008). We have not identified any studies examining quality of life solely in adult survivors of HSCT for PID. Within the HSCT population as a whole, problems with sleep, levels of fatigue/energy, sexual functioning, memory and psychological functioning are reported following transplant (Andrykowski et al., 1997; Bush et al., 1995; Heinonen et al., 2001; Syrjala et al., 2004; Syrjala et al., 2005). It is known, for other populations, that medical late effects and chronic physical health problems can impact quality of life and/or psychosocial outcomes (Kentish & Mance, 2008; Moss & Rosser, 2008; NICE, 2009; 2013; Nyman et al., 2010). There is also growing evidence to suggest that having a genetic condition in the family can provide an emotional burden (McAllister et al., 2007). The degree to which these factors impact on outcomes in PID patients is unknown. From preliminary analysis of a cohort of 40 adult patients who received HSCT for PID, we identified a high rate of psychological morbidity. Over 30% required formal referral for depression or anxiety and 20% are unemployed or work limited, part-time jobs as a result on-going medical and psycho-social morbidity. Further detailed assessment is required to better understand the factors that contribute to these outcomes. In the development of this study, a focus group including patients, parents and members of patient groups also highlighted the need for greater information about quality of life post-transplant. Participants reported that they were given estimates of survival rates but that these did not provide a full representation of life following HSCT. Further information would additionally improve service delivery through the provision of psychological interventions and genetic counselling.

Medical Service Usage and costs borne by patients and families

Recognition of late effects of HSCT had led to the development of guidelines for the long-term follow up of patients receiving allografts for malignancy which recommend extensive and costly screening protocols (Majhail et al., 2012; Socie et al., 2003). Similarly, life-long surveillance is recommended for patients transplanted for PID (Eapen, 2012) to detect and prevent late complications, but data to inform specific guidelines is lacking. Furthermore, the cost-benefit of extensive screening is unclear because the risk of specific problems is unknown and no research has examined the current medical services usage of this population.

Aim

The overall aim of this project is to evaluate the long-term health outcomes of adult patients who underwent Haematopoietic Stem Cell Transplant (HSCT) for Primary Immunodeficiency during childhood, and to identify factors associated with long-term health outcome. In line with the World Health Organisation (1948) definition of health the study has been designed to look at outcome in a holistic way. Within this aim there are **five main objectives**:

1. To examine the mental health outcomes of patients following HSCT. This will document the psychological symptoms and cognitive functioning of this population, compared to a control group and general population norms. It is hypothesised that there will be high variability in psychological and cognitive functioning in patients who underwent transplant, and that there will be higher rates of psychological distress and lower cognitive ability compared to population norms.
2. To examine the physical outcome of patients following HSCT. We will determine the full range of physical health needs of adults following HSCT by examining immunological outcome and late effects of transplant. It is hypothesised that physical outcome contributes to psychological functioning and social outcomes in patients following HSCT.
3. To examine the social outcomes of patients following HSCT, including employment, relationships and socioeconomic status. It is hypothesized that a significant proportion of

patients will have altered social outcomes compared with population norms and the control group.

4. To examine the mediating and moderating factors of health outcomes (e.g., physical, mental and social) in patients with primary immunodeficiency following HSCT. This will aim to establish the factors that impact on poor and good outcomes in this population. It is hypothesized that:

    a. there will be an association between cognitive function and social outcomes;
    b. there will be an association between psychological distress and social outcomes;
    c. that patients experiencing greater physical difficulties will report higher levels of psychological difficulties;
    d. and that patients reporting physical and psychological complications following transplant will experience more limitations in their social circumstances.

5. To measure health service utilisation and costs of adult survivors of HSCT compared with the control group, and factors associated with such usage. We will also measure costs borne by patients and families.

Method

Research Design

The study will employ a cross-sectional and cohort design, examining the current functioning of adult patients who underwent HSCT during childhood and comparing it with healthy controls and population norms.

Participants

Inclusion Criteria: All patients aged 16 and over who have had an HSCT at Great Ormond Street Hospital five years or more previously.

Exclusion Criteria: There are no exclusion criteria. Patients with learning difficulties, who have low levels of literacy or limited verbal communications skills will be supported by family members or carers to complete as much of the assessment pack as possible. All potential participants are known to the clinical team and, if able to communicate verbally, speak good English.

Control Group: The control group will be recruited from siblings of affected patients, or by asking patients to nominate a close friend. Where multiple matching options are available patients will first be matched for gender, then age. This control group was chosen to control for social factors known to be different in this population compared to other chronic illness groups (e.g., higher rates of black and minority ethnic individuals).

Procedure & Measures

Recruitment. All patients who underwent HSCT at Great Ormond Street Hospital five or more years previously will be approached (N = 149). The majority of these have transitioned to the Royal Free London prior to turning eighteen and will be attending routine follow-up clinics. Recruitment will be maximised by offering home visits and/or assessments aligned with clinic appointments.

Participants will be approached to participate in the research via post and during routine follow-up clinic appointments or telephone discussion. Control group participants will be invited through discussion with the index patient. All participants will be given an information sheet and will be required to provide informed consent.

Data Collection. For the index patient, data will be collected from current and historical medical notes, through the completion of questionnaires, telephone assessments and a face-to-face psychological assessment. Data will be collected in six domains (see Appendix 1 for the full schedule of measures and assessment):

1. Demographic data. Information on age, sex, ethnicity and English as second language will be collected from medical notes. Socio-economic status will be classified using the Standard Occupational Classification System (OPCS, 1991). This data will be used to examining the factors that impact on overall outcome.

2. Historical data will be gathered in order to investigate the factors that impact on good or poor outcome.
   Pre- and peri-transplant: Data will be gathered from an established detailed transplant specific database and from the medical notes at GOSH to include age at transplant, molecular PID diagnosis, life-threatening medical complications, wellness at transplant (including presence of end organ damage, height, weight and head circumference), type of donor and chemotherapy conditioning. Information about the clinical course prior to and throughout transplant will be based on time spent in hospital, admissions to Paediatric Intensive Care, duration of impaired immunity following HSCT and the development and treatment required for transplant-associated complications (such as acute graft versus host disease). A score of severity of illness prior to transplant will be calculated based on these factors.
   Post transplant: Data will be gathered from medical notes to include post-transplant complications and treatment required, inpatient days and hospital readmissions and number of clinic visits in the year post transplant. As a measure of the 'success' of HSCT, laboratory data for immune reconstitution and chimerism at one year post transplant will be recorded along with need for ongoing medical treatment.
   Social and psychological: Data will be collected for family socio-economic status, consanguinity, family history (in particular other affected family members and sibling order) and a history of sibling death from the same/different condition. To obtain a measure of early cognitive and psychological wellbeing, IQ (Wechsler Pre School and Primary Scale of Intelligence Third United Kingdom Edition, Weschler, 2004; Wechsler Intelligence Scale for Children Third United Kingdom edition, Weschler, 1992), psychological functioning (Strengths and Difficulties Questionnaire; Goodman, 1999) and previous psychology involvement will be recorded.

3. Psychological and cognitive functioning. In order to establish psychological outcomes and investigate the factors that can lead to good or poor outcome, data will be examined through questionnaires and face-to-face psychological assessment. All measures were selected because they are standardised and reliable measures that are widely used with adults with health conditions.
   Psychological functioning: The SF-36 (Ware & Sherbourne, 1992) will be used as an overall measure of quality of life. This is routinely used as a measure of quality of life, particularly in the field of immunology. Measures of anxiety (GAD-7; Spitzer et al., 2006), depression (Patient Health Questionnaire-9; Kroenk, Spitzer & Williams, 2001), fatigue (FACIT-Fatigue, Yellen et al., 1997), and insomnia (Insomnia Severity Index; Morin, 1993).
   Cognitive functioning: Memory, processing speed and attention will be assessed using subtests from the Weschler Adult Intelligence scale – version 4 (Weschler, 2008) in a face-to-face psychological assessment. The assistant psychologist will receive full training and supervision in conducting these assessments.
   Potential mediating and moderating factors: Other factors known to impact on adaption to illness will be assessed using standardised questionnaires: Coping with Illness (Coping with Health Injury and Problems, Endler & Parker, 2000); Tolerance of uncertainty (Intolerance of

Uncertainty Scale; Buhr & Dugas, 2002); Acceptance of Illness (Primary Antibody Deficiency Acceptance & Control Scale; Booker et al., 2007), Appearance Concerns (Derriford Appearance Scale-24; Carr, Moss & Harris, 2005) and Global Stress (Perceived Stress Scale; Cohen, Kamarck & Mermelstein, 1983).

4. Current physical health. In order to measure physical health outcomes, data will be gathered from medical notes, including information on current height, weight, head circumference, and: *The immunological outcome of transplant* will be measured based on laboratory data for immune reconstitution and chimerism and clinical information about infection burden, and presence of autoimmune or inflammatory components of the original PID. Long term complications of the transplant procedure will be measured using the following parameters:
   - Pubertal development, menstrual cycle and gonadal hormone levels
   - Fertility assessed by conception, sperm testing and DEXA scan
   - Presence or absence of chronic graft versus host disease affecting skin, gut, liver or conjunctiva
   - Assessed clinically and with laboratory data
   - Respiratory and cardiac function assessed by lung function, chest x-ray (PA), high resolution chest CT scan (helical slices) and echocardiogram
   - Renal function assessed by laboratory parameters
   - Endocrine function including thyroid function and bone density
   - Hearing assessed by formal hearing testing
   - Dental problems (such as hypodontia or loss of teeth)
   - Specific follow up measures of end organ disease identified in the pre-transplant assessment will be collected on an individual basis: for example clinical and radiological evidence of bronchiectasis.
   - Other physical manifestations such as warts, scarring of skin, hypopigmentation all of which can have significant effects on self-confidence and external perception

   The Inventory of Health Status (Sheridan et al., 1998) will be used as a measure of general health and patients will be asked about their smoking status, current medications, recreational drug use and alcohol intake (AUDIT-C: Bush et al., 1998). The SF-36 (Ware & Sherbourne, 1992) also provides a measure of physical function.

5. Social circumstances. In order to measure social outcomes, information on patient's social circumstances and relationships will be gathered through the completion of questionnaires. Information on education and employment will be gathered using the Work and Social Adjustment Scale (Mundt et al., 2002) and a general questionnaire detailing educational attainment and receipt of benefits. Social situation will be examined using the Social Network Index (Cohen et al., 1997).

6. Health Care Services Usage and costs borne by patients and families. In order to establish the service utilisation of PID patients following HSCT, we will gather health economic data on resource use and costs for a broad range of services, including NHS services in primary (GP, practice and community nurses, contacts with other members of the primary care and community teams) and secondary care (inpatient, outpatient, day case, A&E) and medications, use of social services, absences from work, as well as any other additional costs to the individual or carer. Service use information will be collected retrospectively by the assistant psychologist through a telephone questionnaire over a year long period, on a quarterly basis. A retrospective approach has been chosen in order to collect accurate data whilst minimizing the demand on patients to record information prospectively.

Unit costs for each type of contact will be obtained from routine administrative sources, applied to the volume of resource use data, and summed across all types of contact to calculate total costs per patient over a one year period. Analogous data will be collected from the matched control group. Patients will also be asked about adherence to medical regimes and cancellation or missing of appointments.

For the control group participants, data will be collected through the completion of questionnaires, telephone assessments and a face-to-face psychological assessment. Data will be collected detailing demographic information, social circumstances, psychological and cognitive functioning and health care service usage (measures as detailed in section 1, 3, 5 and 6 above). As areas known to impact on general health, they will also be asked about their smoking status, recreational drug use and alcohol intake (AUDIT-C: Bush et al., 1998) and their weight and height recorded. In order to be able to control for physical health difficulties, the control group will complete the Inventory of Health Status (Sheridan, Mulhern & Martin, 1998) and provide details of current medications. The SF-36 (Ware & Sherbourne, 1992) also provides a measure of physical function.

Following provision of consent, participants will be approached by the assistant psychologist to arrange an assessment. This can take place in the individual's home or to coincide with a medical follow-up appointment. Questionnaire packs will be sent to the participants prior to their assessments for ease of completion, although support to complete the measures can be given by the assistant psychologist during the assessment. Telephone assessments will be arranged at the participants' convenience.

Consent obtained to participate in the study will include agreement to access medical records and to liaise with General Practitioners. As with routine clinical practice, patients will have access to the clinical teams, incorporating medical, nursing and psychological support as necessary. Participants in the control group will be sign-posted to relevant services as required. The assistant psychologist responsible for the collection and scoring of data will have supervisory input from psychology, with links to the medical team as needed.

Data Analysis

Based on participation rates in our previous study (Titman et al., 2008), 80% recruitment rate is estimated, giving a potential sample size of 119.

Based on earlier data of 22 patients, a mean difference of 18 units (sd = 28) in IQ scores was observed between patient and their sibling controls (Titman et al., 2008). This is equivalent to an effect size of 0.65. However, it is anticipated that the effect size is likely to be somewhat smaller for the outcome measures in this study, and an effect size of 0.4 would be the minimum effect size that would be considered clinically meaningful in this group. In order to detect an effect size of 0.4 as statistically significant at the 5% level, with 90% power, 97 pairs are needed. This is within the expected patient cohort of 119 patients.

The significance level has been adjusted to 0.01 to account for multiplicity (as several outcomes are being examined), therefore this increases the required sample size from 69 pairs to 97 pairs. This is still within the expected sample size, after allowing for attrition, etc.

Primary Outcome measures:

- SF-36 PCS (physical function) and SF-36 MCS (psychological function)

Secondary Outcome measures:

- Anxiety – GAD-7 (Spitzer et al., 2006)
- Depression – Patient Health Questionnaire-9 (Kroenk, Spitzer & Williams, 2001)
- Physical health measure – Inventory of Health Status (Sheridan et al., 1998)
- Health service use, NHS costs and costs borne by patients and families

The main outcome measures will be compared to matched controls using paired t-tests, and compared to norms using one sample t-tests.

For the HSCT patient group univariate and multivariable regression analysis will be carried out to measure the association between possible risk factors and the main outcome measures. Risk factors suggested by previous research (such as diagnostic group, admission to PICU, age at transplant, chronic GVHD, type of conditioning regimen, donor type) will be included in this analysis.

Linearity and Normality assumption of regression will be checked in the usual way.

The remaining results will be reported as descriptive statistics

- Cost Analysis: First the additional annual costs associated with childhood HSCT for immunodeficiency will be calculated. This will be combined with the datasets for cases and matched controls and regress annual costs per person against whether or not the person underwent HSCT, controlling for other factors likely to affect costs. Second the factors associated with costs among people who underwent HSCT will be examined, regressing costs per person against time since transplant and diagnosis and other patient characteristics, plus other factors that may affect costs. To account for skewness of the cost data, a generalised linear model with gamma family and log link will be used (Barber & Thompson, 2004).

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Appendices

Appendix 1: Schedule of Measures

Demographic data		
	Age	Medical Notes
	Socio-economic status	Medical Notes – Standard Occupational Classification System (HMSO, 1991)
	English as second language	Medical Notes
	Consanguinity	Medical Notes
Historical data		
	Age at transplant	Medical Notes
	Type of donor	Medical Notes
	Type of conditioning	Medical Notes
	Time spent in hospital	Medical Notes
	Admissions to PICU	Medical Notes
	Molecular diagnosis|Z	Medical Notes
	Wellness at transplant	Medical Notes
	Chimerism	Medical Notes
	Post-transplant complications	Medical Notes
	Time to immunological reconstitution	Medical Notes
	Number of clinic visits in the year post transplant	Medical Notes
	Family socio-economic status	Medical Notes
	Other affected family members	Medical Notes
	History of sibling death from associated condition	Medical Notes
	IQ	Medical Notes – Wechsler Pre School and Primary Scale of Intelligence Third United Kingdom Edition, Weschler, 2004; Wechsler Intelligence Scale for Children Third United Kingdom edition, Weschler, 1992

	Psychological functioning	Medical Notes – Strengths and Difficulties Questionnaire (Goodman, 1999)
	Psychology involvement	Medical Notes
	Severity of illness prior to transplant	Medical Notes (including duration of inpatient stay, PICU admission, Lansky score, presence of organ damage)
Current physical health.		
	Height	Medical Notes
	Weight	Medical Notes
	Growth and development	Medical Notes – height expectancy, age of puberty (also use historical notes)
	Immune reconstitution	Medical Notes – blood test results
	Immunity/infection burden	Medical Notes – no. of serious infections in since transplant/transition divided by number of years
	Fertility complications	Medical Notes – blood test results, sperm test results, DEXA scan results
	Respiratory complications	Medical Notes – lung function results, chest x-ray (PA) results, high resolution chest CT scan results
	Gastrointestinal complications	Medical Notes
	Dermatological complications	Medical Notes
	Cardiac complications	Medical Notes – echocardiogram results
	Hearing complications	Medical Notes – hearing test results
	Visual complications	Medical Notes
	Dental complications	Medical Notes
	Smoking status	Self-developed Questionnaire - Do you smoke? Yes, No, Ex-smoker?
	Recreational drug use	Self-developed Questionnaire - Do you use recreational drugs? Yes, No, Ex-user?
	Alcohol intake	Standardised Questionnaire – AUDIT-C (Bush et al., 1998)
	General Health	Standardised Questionnaire – Inventory of Health Status (Sheridan, Mulhern & Martin, 1998)
Social circumstances		
	Educational Attainment	Self-developed Questionnaire – Last level of education achieved?

	Receipt of Benefits	Self-developed Questionnaire – Receipt of Employment Support Benefit or Statutory Sick Pay?
	Impact of health on education and employment	Standardised Questionnaire – Work and Social Adjustment Scale (Mundt et al., 2002)
	Social Network and Relationships	Standardised Questionnaire – Social Network Index (Cohen et al., 1997)
	Sexual Functioning	Self-developed Questionnaire – Are you sexually active? Do you experience any problems in your sexual functioning? Are you satisfied with you sex life?
Psychological and cognitive functioning		
	Quality of Life	Standardised Questionnaire – SF-36 (Ware & Sherbourne, 1992)
	Anxiety	Standardised Questionnaire – GAD-7 (Spitzer et al., 2006)
	Depression	Standardised Questionnaire – Patient Health Questionnaire-9 (Kroenk, Spitzer & Williams, 2001)
	Fatigue	Standardised Questionnaire – FACIT-fatigue (Yellen et al., 1997)
	Insomnia	Standardised Questionnaire – Insomnia Severity Index (Morin, 1993)
	Coping with Illness	Standardised Questionnaire – Coping with Health Injury and Problems (Endler & Parker, 2000)
	Tolerance of uncertainty	Standardised Questionnaire – Intolerance of Uncertainty Scale (Buhr & Dugas, 2002)
	Acceptance of Illness	Standardised Questionnaire – Primary Antibody Deficiency Acceptance & Control Scale (Booker et al., 2007)
	Appearance concerns	Standardised Questionnaire – Derriford Appearance Scale 24 (Carr, Moss & Harris, 2005).
	Global Stress	Standardised Questionnaire – Perceived Stress Scale (Cohen, Kamarck & Mermelstein, 1983)
	Enjoyment of Life & Following Dreams	Self-developed Questionnaire – How much are you enjoying life/following your dreams? Likert Scale
	Cognitive Functioning (including memory, processing speed and attention)	Face-to-face Assessment - Weschler Adult Intelligence scale – version 4 (Weschler, 2008). Subtests: Information (general functioning), digit span (working memory), letter number sequencing (attention and concentration), symbol search or coding (processing speed) and matrix reasoning (perceptual reasoning).
Resource Usage		

	Current resource usage, including the number of specialities engaged with and the number of clinic visits/inpatient days in the last year	Client Service Receipt Inventory - self-developed questionnaire by Professor Steven Morris
	Adherence to medical regimes	Self-developed Questionnaire – Approximately how often do you forget to take your medication? Every day, nearly every day, once a week, once a month, once every three months, once a year, never.
	Cancellation or missing appointments	Self-developed Questionnaire – Approximately what proportion of medical appointments have you missed/cancelled in the last year? 0%, 10%, 20% ... 100%