Effectiveness of immunosuppression minimisation, conversion or withdrawal strategies in paediatric solid organ and haematopoietic stem cell transplantation: a protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Paediatric transplantation is the only curative therapeutic procedure for several end-stage rare diseases affecting different organs and body systems, causing posterior great impact in European children’s health and quality of life. Transplanted children shift their primary disease to a chronic condition of immunosuppression to avoid rejection. Longer life expectancy in children poses a greater risk of prolonged and severe side effects related to long-term immunosuppressive (IS) disabilities and secondary cancer susceptibility. The goal remains to find the best combination of IS agents that optimises allograft survival by preventing acute rejection while limiting drug toxicities. This systematic review will aim to determine the optimal IS strategy within the so-called minimisation, conversion or withdrawal strategies.

Methods and analysis We will search the following databases with no language restrictions: Cochrane Central Register of Controlled Trials in the Cochrane Library, OvidSP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; OvidSP Embase Classic+Embase; Ebsco CINAHL Plus, complete database; WHO International Clinical Trials Registry Platform search portal. We will include controlled and uncontrolled clinical trials along with any prospective or retrospective study that includes a universal cohort (all participants from a centre/region/city over a certain period). Cases series and cross-sectional studies are excluded. Two review authors will independently assess the trial eligibility, risk of bias and extract appropriate data points. The outcomes included in this review are: patient survival, acute graft rejection, chronic graft rejection, diabetes, graft function, graft loss, chronic graft versus host disease, acute graft versus host disease, surgical complications, infusion complications, post-transplant lymphoproliferative disease, liver function, renal function, cognition, depression, health-related quality of life, hospitalisation, high blood pressure, low blood pressure, cancer—other, cancer—skin, cardiovascular disease, bacterial infection, Epstein-Barr infection, cytomegalovirus infection, other viral infections and growth.

Strengths and limitations of this study

► The search strategies and lack of dates and language restriction will provide an exhaustive review of the topic.
► The review will cover all types of study designs aiming to capture all relevant information.
► A large number of studies with high risk of bias are expected and they will be clearly analysed.

INTRODUCTION

Background

The treatment of choice for end-stage solid-organ failure in children in most cases is solid organ transplantation (SOT) or haematopoietic stem cell transplantation (HSCT) for the treatment of haematological malignancies, immune-deficiency illnesses or inherited metabolic disorders or haemoglobinopathies. Both SOT and HSCT offer the chance of a cure, but at the same time raise the risk of treatment-related mortality and long-term side effects.

Between 2012 and 2016, 7741 solid organ transplants were performed on children in 23 European Union (EU) countries and 4041 paediatric patients received HSCT.2 3 The clinical consequences of transplantation can be understood as those (i) directly related to
the transplanted organ (acute or chronic allograft rejection, native disease within the allograft, surgical complications), (ii) arising primarily from post-transplant therapies (infection, malignancy, pharmacological toxicity, growth retardation), (iii) linked to the underlying disease (recurrence of original disease in some allografts) and (iv) being multifactorial.

Despite the rate of graft success has improved along with the patient’s clinical outcomes by development and improvements of surgical techniques, anaesthetic procedures and post-transplant care, especially immunosuppression, the patients still need immunosuppressive (IS) agents to prevent rejection of the transplanted organ to a greater or lesser extent whether SOT or HSCT. Therefore, transplanted children have shifted to a chronic condition dependent on IS treatment to avoid grafted organ rejection or graft versus host disease. Consequences of post-transplant IS in children fall into two broad categories: direct organ toxicity and non-specific IS action (ie, infection and malignancy). This chronic condition requires proper monitoring and care of post-transplant complications such as infections, malignancy and chronic rejection, which is even more important in children as they have higher pretransplantation and post-transplantation mortality and morbidity rates than adults.

**Challenges in paediatric transplantation**

IS management is challenging in infants, children and young people. It requires tailored post-transplant management to the unique needs of the youngster. Physiological immaturity of many systems including the immune system, growing and development and other considerations make paediatric transplantation a singular entity when compared with adult transplantation. Diagnostic and therapeutic advances achieved in adult transplant are not necessarily applicable to paediatric transplantation and require a distinct pipeline of development. Specialised clinical and laboratory resources that support the transplantation procedure in common processes such as immunosuppression, immune reconstitution, rejection, tolerance, risk of infection and secondary malignancies are needed in order to accelerate research and new therapies. In addition, other areas of non-medical supportive care are demanded for children and their families, due to severe psychological and socioeconomic issues that extend to adulthood. A paediatric disease affects the whole family, as impairments of a child’s function are a source of emotional distress for parents. Parents of transplanted children have been found to show post-traumatic stress disorder, feeling particularly distressed during the post-transplantation phase. These problems may affect the child’s daily-life function and include a broad spectrum of somatic, psychological and social problems.

Furthermore, despite improvements in short-term graft survival, the immunosuppressive regimens have failed to prolong long-term graft survival, being estimated between 5 and 20 years for SOT and 1–2 years for HSCT. The paediatric transplantation demands even more expertise in reference centres connecting multidisciplinary medical expertise, transfer of knowledge and innovative medicine.

**Minimisation, conversion or withdrawal strategies in paediatric transplantation recipients**

The optimal immunosuppressive regimen maintains graft function (GF), minimising rejection and graft versus host disease while limiting the potential for infection and organ toxicity. The IS treatment for SOT have not changed during the last years. It remains calcineurin inhibitors (CNI) mostly in association with steroids in the short-term and mycophenolate mofetil or mammalian target of rapamycin inhibitors (everolimus, sirolimus) in the mid-term or long term. As mentioned, CNI such as tacrolimus have improved short-term but not long-term graft survival. Prolonged use of IS drugs leads to nephrotoxicity, metabolic disorders, infections and cancer. Biomarkers of tolerance will help us to stratify patients at different stages, tailor and individualise treatment, considering the special characteristics of paediatric patients. In HSCT, IS is withdrawn in most of the patients 1–2 years post-transplantation. Furthermore, limited availability of fully match human leucocyte antigen donors has developed strategies of graft engineering to overcome mismatch related and unrelated donors. In this setting, total T cell depletion, as CD34+ selection, CD3CD19 depletion or partial T cell depletion as αβ T-cell/CD19 B-cell depletion and CD45RA+ depletion, have shown promising clinical results in paediatric patients. The most important issue is that this kind of graft engineering allows the absence of post-HSCT pharmacological prophylaxis early after HSCT.

Strategies to limit the impact of prolonged IS include protocols of drug minimisation towards individualisation of organ-specific immunosuppression regimens, development of new non-nephrotoxic agents and trials of tolerance induction. The lack of consensual and standardised post-transplant care in paediatric patients is also a limitation for the design of clinical trials and for drawing conclusions that can be used in the clinical settings. The small number of SOT and HSCT performed in paediatric patients per year remains a challenge for research in this field, which is even more evident when the analysis is focused on certain organs such as heart and lungs. Some of the limitations of paediatric transplantation are associated with the inability to translate the results obtained from adult studies to paediatric studies examining similar diseases and procedures.

**European reference networks**

The EU, through the 2009 recommendation, advised on the identification of centres of expertise in rare diseases in order to overcome some of the challenges that they face: scarcity of patients, resources and expertise. The multidisciplinary approach of the centres of expertise will improve patient diagnosis, treatments and quality of life (QoL). In March 2017, the EU launched 24 European Reference Networks (ERNs), which are virtual networks
involving healthcare providers across Europe. ERNs were created to tackle rare diseases and complex conditions requiring highly specialised healthcare by gathering knowledge and expertise that will result in better patient care.

ERN TransplantChild is one of the 24 ERNs established in a European legal framework. ERN TransplantChild is the only ERN focused on a complex and highly specialised process, the paediatric transplantation of both SOT and HSCT with a process approach rather than an organ approach. Eighteen healthcare providers from 11 Member States of the EU integrate ERN TransplantChild. The reasoning behind is that paediatric transplantation requires highly specialised centres with highly dedicated and multidisciplinary teams with different transplantation programmes and teams involved including common aspects to all transplants and favouring the implementation of new diagnostic tools and treatments. The network addresses the entire transplant process: pretransplant, transplant and post-transplant phases, dealing with a new chronic condition and preventing secondary transplant-associated diseases. ERN TransplantChild aims at the empowerment and the improvement of life expectancy and QoL for EU paediatric patients requiring a SOT or HSCT or transplanted patients and patients’ families.

In this framework, ERN TransplantChild executive committee decided to develop a clinical practice guideline on the effects of the minimisation, conversion or withdrawal immunosuppression strategies in paediatric solid organ and haematopoietic stem cell transplantation.

OBJECTIVE
To determine the effects of the minimisation, conversion or withdrawal immunosuppression strategies in paediatric solid organ and haematopoietic stem cell transplantation.

METHODS AND ANALYSIS
This systematic review started in April 2020 and was intended to be finished by July 2020.

Criteria for considering studies for this review
Type of studies
This review will consider controlled and uncontrolled clinical trials along with any prospective or retrospective study that includes a universal cohort (all participants from a centre/region/city over a certain period). Cases series and cross-sectional studies are excluded.

Type of participants
The systematic review will include studies on paediatric population (0–18 years) in any stage of the transplantation process: pretransplantation or post-transplantation.

Type of interventions
Any immunosuppression strategy at any stage of the transplantation process, that is, any IS medication used such as steroids, calcineurin inhibitors, mycophenolic acid, sirolimus, everolimus… prescribed to the patients on different regimens or strategies as withdrawal, minimisation or conversion. Biological treatments should be excluded as these are out of the review’s scope. Evaluation of conditioning regimens only should be excluded.

The comparators could be any intervention defined previously or any control. We included, as well, no controlled trials so in this case no comparator could be possible. The uncontrolled cohorts will be used by the CPG panel of experts as complementary information, but the data extracted from those uncontrolled cohorts will not be summarised nor included in the summary of finding tables.

Type of outcome measures
Primary outcomes

- Patient survival: proportion of subjects who are alive after transplantation at any timepoint.
- Acute graft rejection: clinically diagnosed or through biopsy of histological samples so they are not solely based on time of occurrence, are based on the definition from investigators in each of the studies or based on histological samples or clinical diagnose. We will use T-cell-mediated rejection and antibody-mediated rejection, rather than acute and chronic, according to the new Banff classification whenever will be possible. At at least within 6 months from transplantation.
- Chronic graft rejection: clinically diagnosed or through biopsy of histological samples so they are not solely based on time of occurrence, are based on the definition from investigators in each of the studies or based on histological samples or clinical diagnose. We will use T-cell-mediated rejection and antibody-mediated rejection, rather than acute and chronic, according to the new Banff classification whenever will be possible. At at least within 6 months from transplantation.
- Diabetes measured based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose or the 2-hour plasma glucose value after a 75 g oral glucose tolerance test at any time.
- GF:
  - GF kidney: glomerular filtrate rate at any timepoint.
  - GF liver: at least liver transaminases+bilirubin at any timepoint+prothrombin time (PT)+international normalised ratio (INR)+serum lactate+ammonia levels.
  - GF lung: forced expiratory volume in 1 s+forced vital capacity at any timepoint.
  - GF heart: at least ejection fraction at any timepoint and graft vasculopathy.
  - GF intestine: at least citrulline+absorption faecal test at any timepoint.
- GF HSCT: count of leucocytes+platelet+haemoglobin+lymphocytes at any timepoint.
- Graft loss: defined as any medical or surgical condition requiring re-transplantation, such as primary graft dysfunction or non-function and death at any timepoint.
- Acute graft versus host disease: biopsy of histological sample at any timepoint.
- Chronic graft vs host disease: biopsy of histological sample at any timepoint.
- Surgical complications: any complication identified by the investigators.
- Infusion complications: any complication identified by the investigators during the infusion process for stem cell transplantation.
- Post-transplant lymphoproliferative disease (PTLD): biopsy of histological sample at any timepoint.
- Liver function: liver transaminases+bilirubin at any timepoint+PT+INR+serum lactate+ammonia levels.
- Renal function: glomerular filtration rate at any timepoint.
- Cognition measured by the IQ at any timepoint.
- Depression change in depression score from baseline to 6 or 12 months.
- Health-related quality of life (HRQoL): measured using any validated HRQoL scale for children or caregivers.
- Hospitalisation: number of hospitalisations from transplantation at any time point.
- High blood pressure: defined by investigators at any timepoint.
- Low blood pressure: defined by investigators at any timepoint.
- Cancer—other (not skin not PTLD): any cancer identified by investigators at any timepoint.
- Cancer—skin: any skin cancer identified by investigators at any timepoint.
- Cardiovascular disease: any cardiovascular disease identified by investigators at any timepoint.
- Bacterial infection: positive culture.
- Epstein-Barr infection: at least two positive determinations of EBV DNAemia by PCR in blood test and confirmed histologically without evidence of EBV-PTLD. EBV-PTLD should be based on at least two of the following histological features defined by WHO10: (i) disruption of underlying cellular architecture by a lymphoproliferative process, (ii) presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers, (iii) evidence of EBV infection in many of the cells, that is, DNA, RNA or protein. Detection of EBV nucleic acid in blood is not, eo ipso, sufficient for the diagnosis of EBV-PTLD.
- Cytomegalovirus infection/disease: PCR in blood test and confirmed histologically.
- Other viral infections: identified by investigators using PCR, histology, culture or serology.
- Growth: measured using at least height and weight from transplantation to any timepoint.

Secondary outcomes
- Age at transplantation.
- Age of participants at any analysis of primary outcomes provided by the authors of included studies.

Search methods for identification of studies
We will search for all published studies and will review the list of references as well of included studies to find potential relevant studies. All searches will be done from inception until end of March 2019.

Electronic searches
In accordance with the Cochrane handbook, we launched search strategies search for the following electronic databases:
1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 3) in the Cochrane Library.
2. OvidSP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily.
3. OvidSP Embase Classic+Embase.
4. Ebsco CINAHL Plus, complete database.
5. Trial registers:
   1. WHO International Clinical Trials Registry Platform search portal.11
   Search strategy for Medline is in online supplemental Annex I.

Data collection and analysis
Selection of studies
At least two authors from the following list will independently screen titles and abstracts and assess full-text articles from potentially eligible studies:
- Dr Carlos Martín Saborido. IdiPAZ
- Dr Antonio Carcas Sansuán. Hospital Universitario La Paz
- Dr Juan Torres. IdiPAZ
- Dr Alistair Baker. King’s College London KCH Trust
- Dr Caroline Lindemans. Wilhelmina Children’s Hospital
- Dr Daniela Liccardo. Ospedale Pediàtrico Bambino Gesù
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- Dr Dominique Debray. Hôpital Necker-Enfants Malades
- Dr Jacek Toporski. Children’s Hospital, Skåne University Hospital
- Dr Esther Ramos. Hospital Universitario La Paz
- Dr Florence Lacaille. Hôpital Necker-Enfant Malades
Data extraction and management

We will use a standard form to extract data from the included studies. This form will consist of the following fields, but the list could be longer if necessary:

► Study identification.
► Study methods including design, inclusion and exclusion criteria.
► Study population including baseline characteristics.
► Description of the intervention.
► Description of comparator.
► Information for assessment of the risk of bias (RoB).
► Organ/s involved.
► End points.
► Results.

We will use different prespecified forms for each type of study (randomised controlled trial (RCT), non-RCT, uncontrolled trial, cohort studies and case-control studies) and type of outcome (dichotomous or quantitative) in order to capture all relevant information.

One review author will extract data and another one will check all data have been properly extracted. Discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors.

Assessment of risk of bias in included studies

Due to the variety of designs we will find, we have planned to use several tools to assess the RoB. These tools are listed in the table 1.

Two review authors will independently assess each included study for RoB. We will resolve disagreements by discussion and when necessary by consultation with a third review author.

| Name of the tool | Study design |
|------------------|--------------|
| Cochrane RoB tool<sup>13</sup> | Randomised controlled trials |
| RoB criteria for EPOC Reviews<sup>14</sup> (guide for review authors on assessing study quality) | Quasi-randomised trials |
| RoB criteria for EPOC Reviews<sup>14</sup> (guide for review authors on assessing study quality) | Controlled before and after (CBA) studies |
| Risk of Bias in non-randomised Studies of Interventions (ROBINS I)<sup>15</sup> | Interrupted time series studies |
| Risk of Bias in non-randomised Studies of Interventions (ROBINS I)<sup>15</sup> | Cohorts studies |
| Risk of Bias in non-randomised Studies of Interventions (ROBINS I)<sup>15</sup> | Case-controls studies |
| Risk of Bias in non-randomised Studies of Interventions (ROBINS I)<sup>15</sup> | Uncontrolled before and after (CBA) studies |

For dichotomous data, we will calculate Mantel-Haenszel OR from the numbers of events in control and intervention groups. In the case of uncontrolled trials, we will account the number of events in the only group. We also collect 95% CIs or any statistic which allow to calculate the 95% CIs.

If some studies had reported an outcome as a dichotomous measure and others as a continuous measure for the same construct, we will convert results from a relative risk to an SMD, if an approximately normal distribution could be assumed for the underlying continuous measure.

Assessment of heterogeneity

We will explore clinical and statistical sources of heterogeneity among the different groups of studies (RCT, non-RCTs and uncontrolled trials). We will assess statistical heterogeneity using $I^2$ statistics and $\chi^2$ test. We will consider a result to be statistically significant if $p<0.1$. We will consider values of $I^2$ >60% to be an indication of ‘moderate’ heterogeneity and values above 85% to be ‘considerable’ heterogeneity. We may not carry out a meta-analysis if $I^2$ is high and will document the rationale for our decision.

Data synthesis

Where we consider studies sufficiently homogenous in terms of participants, interventions and outcomes, we plan to synthesise results in a meta-analysis using the random-effects model within each of the following groups:

► RCT;
► Non-RCT;
► Uncontrolled trials.

We will perform statistical analysis using the Cochrane Collaboration’s statistical software, Review Manager.
Given the nature of the intervention included, we assume that clinical heterogeneity is very likely to impact on the results of our review, so we will report the random-effects model results, regardless of statistical evidence of heterogeneity in effect size.

Provided we are including three types of interventions/comparators, we will analyse all possible combinations reported.

Subgroup analysis
Results will be analysed for the following subgroups:

- **Type of organ**: heart, intestine, kidney, liver, lung, HSTC.
- **Age groups**: 0–4, 4–8, 8–12, 12–18 years.

Sex is not initially going to be considered, nevertheless if results are clearly disaggregated by sex, we could consider to do a subgroup analysis.

Overall quality of the body of evidence: summary of findings table

The quality of evidence for outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. Quality will be determined as high, moderate, low or very low.

Patient and public involvement

Patient and public involvement (PPI) representatives worked with us to refine the list of outcomes, however, it was difficult to involve patients in other areas of the study design due to the very technical methods required to do design the protocol. PPI representatives will write a plain language summary and design a leaflet for dissemination of the final clinical practice guideline to their peers and distributing to patient groups.

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