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Protocol for updating a systematic review of randomised controlled trials on the prophylactic use of intravenous immunoglobulin for patients undergoing haematopoietic stem cell transplantation

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ABSTRACT

Introduction: Haematopoietic stem cell transplantation (HSCT) is commonly employed in the management of haematological malignancies. This intervention results in an increased risk of infectious and immune-related complications. Prophylactic immunoglobulin therapy has been used to prevent post-HSCT complications, including infections, with varying efficacy. We sought to update the current evidence supporting the use of immunoglobulins in the modern HSCT era.

Methods/analysis: Using a structured search strategy, we will perform a systematic review of the literature from MEDLINE, EMBASE and all EBM Reviews databases. We will include randomised clinical trials investigating clinical outcomes of prophylactic polyvalent immunoglobulin or cytomegalovirus (CMV)-specific immunoglobulin or plasma in patients undergoing HSCT. Clinical outcomes will include overall survival, transplant-related mortality, CMV infection, CMV disease, graft-versus-host disease, interstitial pneumonitis/fibrosis and hepatic veno-occlusive disease. Studies that only reported the results of biochemical tests will be excluded. Data will be extracted by two investigators independently. Study quality assessment will be evaluated using a validated five-point system as proposed by Jadad. Trial quality will be further assessed by identifying whether there was adequate allocation concealment. Where appropriate, a meta-analysis will be performed where relative risk will be used as the primary summary measure with 95% CIs. Pooled measures will be calculated for randomised clinical trials using a random-effects model. The Cochrane Q/χ^2 test and I^2 statistic will also be calculated to evaluate heterogeneity. We will also use a visual inspection of a funnel plot to assess potential publication bias.

Discussion: This systematic review aims to provide current evidence to justify the use of immunoglobulin prophylaxis in HSCT recipients. We will discuss whether current HSCT guidelines are supported by the current evidence, and whether further trials are needed, given the changing landscape of patients undergoing HSCT and the immunoglobulin manufacturing process.

Systematic review registration: PROSPERO CRD42015016684.

Strengths and limitations of this study

- Rigorous study selection, data extraction, quality assessment and data synthesis.
- Predefined a priori sensitivity analyses.
- There may be a limited number of recent trials representing the haematopoietic stem cell transplantation population in the modern era.

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is commonly employed in the management of a variety of malignancies.[1 2] High-dose chemotherapy and/or radiotherapy are given to maximise the tumouricidal effects, followed by the timely infusion of stem cells to reconstitute the bone marrow and immune system. Pancytopaenia and immunodeficiency from therapy may cause potentially fatal bacterial, viral or fungal infections such as cytomegalovirus (CMV) and immune complications such as graft-versus-host disease,[3–5] following transplantation.

Intravenous immunoglobulin (IVIG) is a complex biological product with multiple potential mechanisms of action.[6] IVIG is used in many HSCT centres to prevent infectious complication post-HSCT.[7 8] For instance, at our centre, we have previously reported 31 and 13 doses of IVIG use during the first month post-HSCT in 77 autologous and 39 allogeneic transplant recipients.[9] CMV-specific

immunoglobulin and plasma preparations are also available, and have been reported to be superior to polyvalent IVIG in the management of CMV infections.[10 11] However, a recent systematic review of immunoglobulin prophylaxis did not demonstrate a mortality benefit but, rather, showed an increased risk of a veno-occlusive side effect.[12] Consequently, current societal guidelines do not recommend the routine use of immunoglobulin prophylaxis in recipients of HSCT.[13 14] However, the clinical trials included in the previous systematic review were mostly published before the year 2000.[12] Further, there are other limitations in this review that deserve mention. First, the review included non-randomised studies;[15] second, some studies only looked at biochemical surrogates, which may not correlate with patient relevant 'hard' outcomes and, lastly, results from higher quality studies were not separately analysed, potentially introducing bias. Moreover, the landscape of patients receiving HSCT has evolved in the past decade. Patients undergoing HSCT are older and are more likely to be immunocompromised.[16] Further, HSCT technology including conditioning and chemosuppressive measures has also evolved.[2 17–19] Finally, the technology of immunoglobulin production has evolved, resulting in intact IgG preparations with normal half-life and effector functions, and with higher pathogen safety.[20] Taken together, the prior available evidence may not be adequate to inform current HSCT practice.

We seek to conduct a comprehensive systematic review of available evidence from prospective randomised controlled clinical trials assessing the use of immunoglobulins in HSCT that report clinically important end points.

AIMS AND OBJECTIVES

Our overarching objective is to update, summarise and quantify the clinical effects of prophylactic immunoglobulins in the context of HSCT. Specifically, we seek to evaluate the utility of peri-HSCT use of IVIG on mortality, post-HSCT complications, infections and relapse post-HSCT.

METHODS/DESIGN

Search strategy

The systematic search strategy will include MEDLINE (1966 to February 2015), EMBASE (1980 to February 2015) and all EBM Reviews (December 2014). A Dickersin *et al*[21] filter will be used to aid identification of randomised controlled trials (RCTs). A Google Scholar search will be performed in order to identify any grey literature. Studies relevant to animals but not to humans will be excluded. Publications, regardless of language, and regardless of whether they were published as conference proceedings, abstracts or journals, will be included in our review. Local HSCT physicians will also be approached to identify additional relevant studies/trials. References to selected articles will be examined by two reviewers (JT and JC) to identify relevant citations.

Draft of search strategy

Database: Embase Classic+Embase <1947 to 2015 February >, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1. Hematopoietic Stem Cell Transplantation/
2. h?ematopoietic stem cell transplant$.tw.
3. (hsct or h?ematopoietic sct).tw.
4. stem cell transplant$.tw.
5. Peripheral Blood Stem Cell Transplantation/ or pbsct.tw.
6. (peripheral blood cell transplant$ or peripheral blood stem cell transplant$ or peripheral stem cell transplant$).tw.
7. Bone Marrow Transplantation/ or (bone marrow transplant$ or bmt).tw.
8. blood transplant$.tw.
9. ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
10. or/1-9
11. exp Immunoglobulins/ and (exp Immunization, Passive/ or exp Administration, Intravenous/ or exp Injections, Subcutaneous/ or exp Infusions, Subcutaneous/)
12. Immunoglobulin$.tw.
13. Immune Globulin$.tw.
14. (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
15. or/11-14
16. 10 and 15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. random$.tw.
20. placebo.ab.
21. clinical trials as topic.sh.
22. trial.ti.
23. or/17-22
24. animals/ not humans/
25. 23 not 24
26. 16 and 25
27. guideline.pt.
28. practice guideline.pt.
29. guidelines as topic/ or practice guidelines as topic/
30. guideline$.tw.
31. 27 or 28 or 29 or 30
32. 16 and 31
33. 26 or 32
34. 33 use prmz
35. exp hematopoietic stem cell transplantation/
36. h?ematopoietic stem cell transplant$.tw.
37. (hsct or h?ematopoietic sct).tw.
38. stem cell transplant$.tw.
39. peripheral blood stem cell transplantation/
40. pbsct.tw.
41. (peripheral blood cell transplant$ or peripheral blood stem cell transplant$ or peripheral stem cell transplant$).tw.
42. bone marrow transplantation/
43. (bone marrow transplant$ or bmt).tw.

44. blood transplant$.tw.
45. ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
46. or/35-45
47. exp immunoglobulin/iv, sc [Intravenous Drug Administration, Subcutaneous Drug Administration]
48. exp immunoglobulin/ and (intravenous drug administration/ or subcutaneous drug administration/ or passive immunization/)
49. immunoglobulin$.tw.
50. Immune Globulin$.tw.
51. (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
52. or/47–51
53. 46 and 52
54. random$.tw. or placebo$.mp. or double-blind$.tw.
55. practice guideline/
56. guideline$.tw.
57. 54 or 55 or 56
58. 53 and 57
59. 58 use emczd
60. 34 or 59
61. remove duplicates from 60
62. 61 use prmz Medline Search
63. 61 use emczd Embase Search

Inclusion and exclusion criteria

Inclusion criteria will be prospective randomised controlled clinical trials, patients undergoing HSCT, patients receiving polyvalent IVIG or subcutaneous immunoglobulin, or CMV-specific immunoglobulin or plasma (CMVIG) prophylaxis, use of a comparator arm, studies reporting clinical outcomes of overall survival (primary outcome), transplant-related mortality, CMV infections, CMV diseases, non-CMV infections including bacterial, fungal, other viral infections, graft-versus-host disease, interstitial pneumonitis veno-occlusive disease and relapse of the underlying haematological condition. Studies that only reported the results of biochemical tests will be excluded from our review given the potential that it may not correlate with patient centred hard outcomes.

Outcome measures

Primary outcome: Overall survival is defined as survival with varying subsequent follow-up times as defined by the individual studies (at least 100 days).

Secondary outcomes: (1) Transplant-related mortality; (2) CMV infection; (3) CMV disease; (4) non-CMV infection, which will be further stratified to bacterial, fungal and other viral infection; (5) hepatic veno-occlusive disease, broadly defined as weight gain or fluid accumulation, elevated bilirubin and abdominal pain; (6) graft-versus-host disease and interstitial pneumonitis/fibrosis, defined by the individual studies and (7) disease relapse.

Definition

Transplant related mortality=death within 100–120 days of HSCT

CMV infection=recovery of the virus from the throat, urine or blood, seroconversion of a patient or significant increase in CMV viral copies in the absence of any clinical signs or symptoms of disease

CMV disease=symptomatic infection, recovery of virus from a visceral site or histological evidence of infection

Bacterial infection=reported infection due to microbiologically confirmed bacteria

Viral infection=reported infection due to microbiologically confirmed virus other than CMV

Fungal infection=reported infection due to microbiologically confirmed fungus

Data extraction

Two reviewers (JT and JC) will independently review the abstracts and apply our trial eligibility criteria. Any discrepancies will be documented, discussed and adjudicated by a third party (DWC). The two reviewers (JT and JC) will assess trial quality and extract the data using a standardised data abstraction form and data entry onto Microsoft Excel, to assist with data management. Similarly, discrepancies will be documented, discussed and adjudicated by a third party (DWC).

Quality assessment

The methodological quality of randomised studies will be evaluated by two reviewers (JT and JC) using a validated five-point system as proposed by Jadad.[22] A quality score of 3 or greater will be considered high quality.[22] Trial quality will be further assessed by identifying whether there was adequate allocation concealment.[23] The quality of evidence across studies will be assessed for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Risk of bias assessment

The following domains of potential bias will be assessed by two reviewers (JT and JC) and any discrepancies will be discussed and adjudicated by DWC and GK: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and personnel); and (3) detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting).

Data analysis/synthesis

Relative risk will be used as the primary summary measure with 95% CIs. Pooled measures will be calculated for randomised clinical trials using a random-effects model. A relative risk of <1 would suggest a beneficial effect of IVIG, while a relative risk of >1 would suggest a harmful effect. Individual trial estimates and pooled estimates will be performed using Review Manager software (Cochrane Collaboration's Information Management System).[24] The Cochrane Q/χ^2 test and I^2 statistic will also be calculated to

evaluate heterogeneity. We will use a visual inspection of a funnel plot to assess potential publication bias.[25 26]

We will perform several a priori sensitivity analyses to understand the data and to identify any subpopulations that may benefit from the use of IVIG. These analyses include: type of HSCT (autologous or allogeneic), conditioning regimen, indication for transplant, type of IVIG used (IVIG or CMVIG), dose of IVIG used (≤2, >2, ≤5 and >5 g/kg), IgG levels (IgG <4 g/L and ≥4 g/L), methological quality of RCTs (Jadad scores ≥3 or <3), as well as year of publication of the study (before or after 2000).

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination.

DISCUSSION

A systematic review of immunoglobulin prophylaxis in HSCT published in 2009 analysed 30 studies.[12] Some were not RCTs, or they only measured biochemical test results. Most studies (25/30) were published before the year 2000, when patients were less complex. The current guidelines[14] recommended against use of prophylactic IVIG in HSCT, although IVIG prophylaxis may be considered in patients with severe hypogammaglobulinaemia (IgG <4 g/L). The latter statement was not supported by strong evidence.

Our systematic review will update the current evidence on the use of immunoglobulin prophylaxis and may stimulate a re-evaluation of our current practice and practice guidelines. It is likely that the available data are outdated, and more current randomised trials are required to inform practice.

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Contributors JC drafted the protocol. JT critically reviewed and revised the protocol and the guarantor. JC and JT performed the data extraction, data interpretation and manuscript preparation. JT, DWC and GK were consulted for the interpretation of results and preparation of the manuscript. All the authors conceived and designed the review, and read and approved the final manuscript.

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