DSEN ABSTRACT

A Systematic Review Comparing Interventions for the Prophylaxis and Treatment of Graft Versus Host Disease in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Summary

- Evidence from randomized trials is lacking or of limited size for many comparisons between GVHD prophylactic and treatment regimens used for patients undergoing HSCT. Overall, inconsistency in measurement and reporting of outcomes, limited connectivity of evidence networks and between-study clinical heterogeneity limited the capacity for network meta-analyses, with the number of regimens compared varying by outcome.

- **GVHD prophylaxis.** Prophylactic regimens that reduced risk of acute or chronic GVHD were associated with increased risk of disease relapse. MTX+TAC may represent a regimen providing the best balance of benefits and risks.

- **GVHD treatment.** Response to the treatment of acute GVHD may be improved with the use of mycophenolate mofetil + steroids; however, overall survival may be compromised. This regimen warrants further study. For treatment of cGVHD, no therapy was found to be superior to steroids alone.

What is the issue?

- Graft-versus-host disease (GVHD) is a potentially life-threatening complication that frequently occurs following allogeneic hematopoietic cell transplantation (HSCT). Matching of donor and recipient for major histocompatibility antigens reduces the risk of development of GVHD; however, 35–40% of fully matched recipients will still develop acute GVHD (aGVHD) due to unmatched minor histocompatibility antigens. To further reduce the risk of GVHD, various GVHD prophylactic and treatment strategies have been developed. The ideal strategy to prevent or treat GVHD is unknown.

What was the aim of the study?

The following objectives were addressed:

1. To compare the benefits (i.e., prevention of GVHD) and harms (e.g., risk of relapse, infection, and mortality) of competing regimens for prophylaxis of GVHD in patients undergoing HSCT, and to establish a hierarchy of intervention strategies according to their efficacy and safety.
2. To compare the benefits (i.e., resolution of GVHD) and harms (e.g., risk of relapse, infection, and mortality) of competing regimens for treatment of GVHD in patients undergoing HSCT, and to establish a hierarchy of intervention strategies according to their efficacy and safety.

How was the study conducted?

- Medline, PubMed, Embase, and the Cochrane Register of Controlled Trials were searched in 2013 for randomized trials of patients undergoing HSCT. Searches were updated in 2015 and 2017. Studies were included if patients underwent allogeneic HSCT in the treatment of hematologic neoplasias or benign disease and were randomly allocated to receive a pharmacological intervention for the prophylaxis or treatment of acute or chronic GVHD. Outcomes of interest included overall mortality, relapse of underlying disease, incidence of acute and chronic GVHD (prophylaxis review), resolution of acute and chronic GVHD (treatment review), and specific harms. We conducted separate analyses for the prophylaxis and treatment of GVHD, using Bayesian network meta-analysis to compare interventions for outcomes of interest, where feasible. For outcomes for which network meta-analysis were not possible, detailed narrative summaries were prepared.

What did the study find?

- Thirty-two trials assessed 19 unique GVHD prophylactic regimens in 3,875 patients. Seven trials assessed 10 unique treatment strategies for aGVHD (four studies) and chronic GVHD (cGVHD) (three studies) in 830 total patients. Overall, there was substantial variability in patient populations with respect to age, underlying hematologic disease, disease risk of relapse/mortality, and transplant donor status (i.e., related vs. unrelated, matched vs. unmatched). Trial publication dates ranged from 1979–2015. Methotrexate (MTX)+tacrolimus (TAC) was considered the standard GVHD prophylaxis for comparison purposes.

- **GVHD Prophylaxis (RQ1):** Most network comparisons were based on only indirect evidence and single studies. Compared to the reference treatment MTX+TAC, data suggest that MTX+TAC+sirolimus (SIR) and SIR+TAC were superior for prevention of aGVHD. Treatment rankings suggested MTX+TAC+SIR was best, though differences were minimal compared to SIR+TAC, CsA+MTX+mesenchymal stem cells and MTX+TAC+steroids. For the prevention of cGVHD, cyclosporine (CsA)+MTX+anti-thymocyte globulin (ATG)+steroids was superior to almost all other regimens. Generally, regimens that were associated with favourable acute and chronic GVHD outcomes were associated with a less favourable relapse outcome at 2–3 years. As well, regimens of single agents were less efficacious to prevent GVHD than regimens involving multiple agents; however, single-agent regimens generally were more efficacious at preventing relapse of underlying disease. Regimens containing a calcineurin inhibitor (i.e., TAC or CsA) had greater efficacy to prevent aGVHD than regimens without; however, there was no significant difference between TAC- or CsA-containing regimens. Single studies suggest that the addition of ATG may reduce cGVHD may not increase overall mortality or relapse; however, it can increase CMV reactivation. The available evidence suggests that MTX+TAC may provide the best balance of benefits and risks for GVHD prophylaxis.
- **GVHD Treatment (RQ2):** Network meta-analyses were not feasible due to the small number of studies split between treatment of aGVHD and cGVHD, inconsistently reported outcomes and high between-study heterogeneity. Thus, narrative synthesis was employed. Mycophenalate mofetil (MMF)+steroids was superior to etanercept+steroids in the treatment of aGVHD after 28 and 56 days of follow-up, and steroids alone were superior to alemtuzumab (ALZ)+steroids in the treatment of cGVHD after nine months. No other comparisons were associated with statistically significant differences between regimens. Compared to steroids alone in the treatment of aGVHD, MMF+steroids resulted in increased overall mortality, but not non-relapse mortality, after one year of follow-up. Similarly, when MMF was added to steroids+either CsA or TAC or SIR, overall mortality was increased, but not non-relapse mortality, after four years of follow-up. When ALZ was added to steroids, greater non-relapse mortality, but not overall mortality, occurred after four years of follow-up.

Authors: Dianna Wolfe, Brian Hutton, David Moher, Fatemeh Yazdi, Chris Bredeson, Natasha Kekre, David Allan.

For more information, please contact Brian Hutton, bhutton@ohri.ca

This research was funded by CIHR – Drug Safety and Effectiveness Network and conducted by investigators affiliated with the following institutions:

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Ottawa Hospital Research Institute / Institut de recherche de l'Hôpital d'Ottawa

Link to publication: Hutton et al, 2015.