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What Causes Aplastic Anaemia?

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Aplastic anaemia has diverse etiologies including; (1) direct damage to haematopoietic stem or progenitor cells such as from chemicals, drugs and ionizing radiations; (2) an abnormal bone marrow micro-environment, (3) immune-mediated mechanism(s); or (4) combination of these. Aetiologies may differ between persons with similar phenotypes and even genotypes[1](References in Supplement). These aetiologies are not mutually exclusive and can be tested, in part, by analyzing results of haematopoietic cell transplants

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Authour Contributions RPG and ME designed the study. Statistical analyses were done by KMH and MH. RPG and LB prepared the initial typescript with edits from all authors. All authors reviewed and accept responsibility for the final typescript and agree to submit for publication.

Data Use Statement

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

between genetically-identical twins one of whom has aplastic anaemia. Recovery of bone marrow function after transplanting haematopoietic cells from a twin without pretransplant conditioning favours damage to haematopoietic stem or progenitor cells as the aetiology and suggests a bone marrow micro-environment abnormality is an unlikely aetiology. It also likely excludes a congenital abnormality as aetiology because the donor twin has normal bone marrow function. In contrast, failure to recover after a 1st unsuccessful transplant without pretransplant conditioning, but recovery after a 2nd transplant with it sometimes combined with posttransplant immune suppression, favours an immune aetiology.

There are several reports of genetically-identical twin transplants for aplastic anaemia, mostly of few subjects or with contradictory outcomes[2–10] A prior Center for International Blood and Marrow Transplant Research (CIBMTR) study analyzed data from 40 subjects with aplastic anaemia receiving genetically-identical twin transplants from 1964–1992 with and without pretransplant conditioning[4]. About one-third of recipients of a twin transplant without pretransplant conditioning recovered normal bone marrow function; the remainder did not.

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin (MCW). The CIBMTR Research Database includes long-term clinical data of more than 600,000 subjects from more than 330 centers worldwide. Accuracy of reported data and compliance are monitored by on-site audits. The Institutional Review Board of the National Marrow Donor Program approved the study and consent is sought from subjects and/or their legal guardians for research.

We interrogated data from 59 consecutive subjects with aplastic anaemia receiving a 1st haematopoietic cell transplants from a genetically-identical twin between January 1, 2000 to December 31, 2019. Subjects received bone marrow or blood cell grafts. Although we refer to this as a *transplant*, it can also be considered an *infusion*. The outcome of interest was bone marrow recovery defined as a granulocyte concentration >0.5 × 10E+9/L and a platelet concentration >20 ×10 10E+9/L for 3 consecutive days. In some instances there was recovery to a normal granulocyte concentration but not recovery to a normal platelet concentration. Analyses are descriptive. Median follow-up of 6 years (range, 0.5–18 years).

Subject-, disease- and transplant-related co-variates are displayed in Supplement Table 1. Subjects were divided into those in whom a 1st transplant was preceded (N = 11) or not (N = 48) by pretransplant conditioning with or without posttransplant immune suppression. 38 subjects were male. Median age was 18 years (IQR 11–32 years). Median interval from diagnosis to 1st transplant was 2 months (IQR 1–3 months). 33 subjects received no immune suppression in the interval before starting their transplant whilst 9 failed prior immune suppression therapy mostly with cyclosporine and antithymocyte globulin (ATG) with or without corticosteroids. Pretransplant conditioning for a 1st transplant was predominately cyclophosphamide (N = 45) with (N = 33) or without other drugs including ATG (N = 19), fludarabine (N = 5), fludarabine plus ATG (N =3), busulfan (N = 3) or ionizing radiation (2–10 Gy; N = 3). 1st grafts were bone marrow (N = 33) or mobilized blood cells (N = 26). 27 recipients of a 1st transplant with pretransplant conditioning received posttransplant

immune suppression with a calcineurin-inhibitor alone (N = 14) or with methotrexate (N = 12) or mycophenolate mofetil (N = 1).

9 of 11 subjects of a 1st transplant without pretransplant conditioning had data reported on granulocyte and platelet recovery – 6 initially recovered both, 2 recovered granulocytes but not platelets and 1, neither. Only 2 recipients had a sustained granulocyte concentration >0.5 × 10E+9/L. The 9 subjects whose first infusion failed to restore normal bone marrow function received a 2nd transplant using the same twin donor with pretransplant conditioning. 7 recovered the target granulocyte and platelet concentrations. 2 subjects who did not recovered after their 2nd transplant, 1 with early and 1 with late declines in granulocyte concentrations received cyclophosphamide and ATG without additional posttransplant immune suppression before their 2nd transplant (Supplement Table 2).

In subjects receiving pretransplant conditioning before their 1st transplant, 46 had data reported on granulocyte recovery and 41 on platelet recovery. All had initial granulocyte recovery and 41, initial platelet recovery. However, granulocytes declined in 7, all of whom subsequently recovered normal bone marrow function after receiving a transplant from an HLA-matched sibling donor (N = 3) or the same genetically-identical twin donor.

Graft-*versus* host disease (G*v*HD) was reported in 7 subjects. Neither acute nor chronic G*v*HD was reported in the 11 subjects transplanted without pretransplant conditioning. Subjects receiving pre-transplant conditioning were reported to have acute G*v*HD ≥ grade-2 and 4 were reported to have chronic G*v*HD. All subjects transplanted without pretransplant conditioning survived; 45 of 48 subjects transplanted after receiving pretransplant conditioning survived.

Our data indicate few recipients of a haematopoietic cell transplant from a genetically-identical twin without pretransplant conditioning recover normal blood granulocyte concentrations. In contrast, most recover when a 2nd transplant is preceded by pretransplant conditioning. Genetically-identical twins whose 1st transplant was preceded by conditioning more often recovered normal bone marrow function. These data suggest direct damage to haematopoietic stem or progenitor cells is an unlikely aetiology of many cases of aplastic anaemia. Because most subjects failing their 1st transplant without pretransplant conditioning recovered after a 2nd transplant with pretransplant conditioning, an abnormal bone marrow micro-environment also seems an unlikely aetiology but cannot be excluded as pretransplant conditioning might alter the bone marrow micro-environment.

Several subjects had complete granulocyte recovery but only partial platelet recovery. Because the lifespan of granulocytes is much briefer than platelets, granulocyte recovery is a better surrogate for recovery of bone marrow function. Additionally, some recipients of successful haematopoietic cells allotransplants have impaired platelet recovery despite otherwise normal bone marrow function and complete haematopoietic chimerism. Diverse reasons for impaired platelet recovery are reviewed elsewhere[11–13].

Although the data presented here seemingly differ from our prior study where 7 of 23 subjects recovered bone marrow function without pretransplant conditioning *versus* 2 of 11, this difference is not statistically significant ($P = 0.73$ with Yates correction)[4].

There were several unexpected findings in our study. 1st, several subjects were reported to develop acute and/or chronic G*v*HD. Whether this is possible is controversial[14]. 2nd, many subjects received posttransplant immune suppression, presumably to prevent G*v*HD, despite transplants from presumed genetically-identical twins. Whether donors were really genetically-identical twins cannot be known with certainty as genetic-identity of twins is a probabilistic estimate based on potentially informative genetic loci. Additionally, the CIBMTR relies on centres to report presence of G*v*HD and this can be subjective and confounded by heuristics[15–22]. Incorrect diagnosis of chronic G*v*HD seems far less likely but a syndrome resembling chronic GvHD is reported in rats receiving syngeneic grafts in the context of posttransplant cyclosporine[23].

There are important limitations to our study arising from using an observational database. 1st, there are relatively few subjects. However, our cohort likely represents most genetically-identical twin transplants for aplastic anaemia done in the US. 2nd, we relied on reporting from centres to identify the donor as haematologically normal. 3rd, without an artificially introduced genetic marker, it is impossible to determine whether posttransplant bone marrow recovery is from the donor, recipient or both. Lastly, we do not know why some subjects received pretransplant conditioning before a 1st transplant and others did not. This may have resulted in a selection biases. Similarly, we do not know why some reportedly genetically-identical twins received posttransplant immune suppression. Because graft-rejection cannot occur between genetically-identical persons preventing this cannot be the reason. In addition, why some subjects received immune suppression before attempting a transplant and others did not is unknown. And we do not know what proportion of persons with a genetically-identical twin recovered after receiving interventions other than a transplant. Given these limitations one should not use results of our analyses to identify a preferred transplant strategy for persons with aplastic anaemia with a genetically-identical twin.

In conclusion, our data indicate transplanting normal haematopoietic cells from a presumed genetically-identical twin without pretransplant conditioning rarely results in recovery of normal bone marrow function. These data are consistent with the hypothesis relatively few cases of aplastic anaemia are caused by direct damage to haematopoietic stem or progenitor cells. The data are also consistent with the hypothesis that an immune aetiology underlies most cases of aplastic anaemia although bone marrow microenvironment abnormalities cannot be excluded.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

RPG is a consultant to NexImmune Inc. and Nanexa Pharma Ascentage Pharm Group, Antengene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd. CCD reports consulting for Alexion, Inc., Omeros Corp., and Jazz Pharmaceuticals. ARG reports a non-restrictive educational grant from Jazz Pharmaceuticals to conduct a study “Role of endothelial cell damage and activation in idiopathic pneumonia syndrome post stem cell transplantation”.