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Authors
Butte, Manish J
Kobayashi, Roger H

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Editorial

An Updated Survey of SCID Outcomes Without Preconditioning Chemotherapy

Manish J. Butte, MD, PhD, and Roger H. Kobayashi, MD *Los Angeles, Calif*

Severe combined immunodeficiency (SCID) is a collection of rare genetic disorders that exhibit an inability of infants to generate a useful repertoire of T cells and thus characterized by heightened susceptibility to infection. Dr Buckley's center at Duke University has almost peerless experience in the management of SCID by allogeneic transplantation, and they offer in this issue[1] an update of their cohort since their last article in 2009.[2] The unique aspect of Duke's cohort, treated from 1982 to 2019, is that no patient received pretransplant chemotherapy (also called "conditioning") or posttransplant prophylaxis for graft versus host disease. The specific questions being examined relate to the initiation of transplantation before age 3.5 months versus after, an arbitrary line that has been widely used since this group and the team from Great Ormond Street Hospital published in groundbreaking work that early transplant resulted in excellent survival, findings based on the diagnosis at birth of babies with family histories of SCID.[3,4] As expected, here Hardin et al[1] showed that the survival of infants at Duke was higher among those transplanted early in life (94%) versus late (68%). These survival data are quite akin to other recently published collections.[5] Direct head-to-head comparisons were not made, but these results suggest that at least when considering long-term survival after hematopoietic stem-cell transplantation for SCID, conditioning may not be required.

So what does conditioning offer? It has been well established that conditioning improves engraftment (as measured by myeloid chimerism),[5] and importantly, propels the development of donor B cells after transplant. Alas, more than half the patients in the Duke cohort required ongoing immunoglobulin replacement.[1] This proportion is notably higher than that observed in centers that routinely use conditioning.[5] Recent analyses suggest that B-cell development improves with even modest amounts of conditioning chemotherapy resulting in modest levels of myeloid engraftment, and that the genetic lesions that impair B-cell development benefit the most from chemotherapy.[6] Although the use of chemotherapy for conditioning may improve outcomes for B cells, there is on the flip side the potential for considerable toxicities, including dental disease, thyroid disease, and difficulties in growth. Unfortunately, this article from Hardin et al[1] did not explore whether any of these concerns were alleviated in their large cohort of patients who never received chemotherapy. Thus, there are still opportunities to explore whether transplant-associated toxicities can be improved by "reduced-intensity" conditioning or no conditioning at all. Quantitative trade-offs in terms of costs and alterations of quality of life with regard to chemotherapy and continual immunoglobulin replacement remain to be seen. Careful assessment of large cohorts for neurodevelopmental outcomes, accessibility of doctors, and affordability of ongoing care are needed. For patients with congenital agammaglobulinemia, the costs of lifelong immunoglobulin replacement are surprisingly higher than those of transplantation.[7]

The quantum shift in our clinical care of SCID occurred over the past 10 years as each state incorporated newborn screening (NBS) for SCID into clinical practice. North Carolina began to screen for SCID in 2015. On the basis of the population, one might surmise that 5% to 10% of the 177 patients of the Duke cohort were identified by NBS, and these infants would be most likely to get transplanted before age 3.5 months. It is quite unfortunate that this work did not explore the impact of NBS on the numbers of transplanted infants, their age at transplantation, prevention of infection before transplant, or transplant outcomes.

In particular, the motive force behind NBS for SCID lay in its well-documented ability to initiate transplantation before life-threatening infections have taken ahold. Many of us vividly remember the era when SCID was diagnosed in critically ill 6-month-olds in the pediatric intensive care unit. Infections historically posed a major barrier to engraftment and survival. Many infections can indeed be avoided by early diagnosis (namely, NBS).[5,8] Unexpectedly, however, improvements in mortality of babies with SCID hit a limit despite early diagnosis and transplant, and early infections from cytomegalovirus (CMV) are a major culprit.[5,8] Primary CMV infections of people with pregnancy and consequent perinatal vertical transmission are very rare. Instead, CMV is most likely transmitted to newborns with SCID through intermittent shedding in the breast milk.[9] Breast-feeding begins (or should begin) right after birth, while even the most expeditious newborn screening program requires a few days to measure low T-cell receptor excision circles and direct the baby to a referral center. In California, we have instituted a policy to halt breast-feeding immediately on learning that T-cell receptor excision circles are critically low, but even that strategy still allows exposure of the baby to 5 to 10 days of unabated breast-feeding. Hardin et al's work shows that 9 of 48 (almost 20%) deaths in their cohort were due to CMV, highlighting this concern. Unfortunately, their work did not

Department of Pediatrics, Division of Immunology, Allergy, and Rheumatology, University of California Los Angeles, Los Angeles, Calif

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Corresponding author: Manish J. Butte, MD, PhD, 10833 Le Conte Ave, MDCC Building Rm 12-430, Los Angeles, CA 90095. E-mail: mbutte@mednet.ucla.edu.

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characterize whether the CMV infections occurred early (eg, perhaps via breast milk) or late (eg, nosocomial or community-acquired infection), in the NBS population versus those diagnosed after the onset of infections, or in those babies who received breast milk versus those who may have been formula-only fed. How to prevent the earliest exposures to CMV remains an unsolved problem in SCID.

Overall, care for SCID continues to improve, and this latest milepost from Duke tells us how far we have come. Indeed, the endurance of Dr Buckley's team combined with the longevity of the Duke cohort allow us to calibrate our sense of progress over the decades. The next decade will bring exciting changes in the diagnosis and management of SCID, both evolutionary (eg, individual pasteurization of breast milk to eliminate CMV[10]) and revolutionary (eg, chemotherapy-free, antibody-based conditioning and widespread availability of gene therapies). We look forward to updates from the Duke cohort as these new changes make their way into clinical care.

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