

microvascular constriction to any given thermal stimulus in SCD patients and a cumulative decrease in perfusion with repeated thermal stimulation specific to SCD that did not recover within the experimental time frame (see figure). Although decreased microvascular blood flow does not necessarily result in vaso-occlusion, autonomic hyperresponsiveness to thermal stimulation or pain anxiety is an original observation in SCD that may help explain vaso-occlusion and offer new therapeutic targets.

SCD is characterized by a remarkable phenotypic heterogeneity that can only partly be explained by genetic factors.⁵ Environmental factors are thought to play an important role, but studies have shown conflicting results.⁶ Despite the empirical evidence of an increase in vaso-occlusive pain after exposure to cold, for instance, no clear association has been shown. The findings in the Veluswamy et al study potentially bridge the gap between triggering environmental factors and the occurrence of vaso-occlusive events. In patients prone to vasomotor hyperresponsiveness, environmental exposure to cold results in progressive decreased perfusion, and a small additional factor such as stress may be sufficient to further decrease regional perfusion and trigger vaso-occlusion. The reflex vasoconstriction response to stimuli involves neural-mediated mechanisms that ultimately lead to the release of norepinephrine and neuropeptide Y as vasoconstrictors.⁷ However, other key biological factors may also modulate the response to these thermal stimuli. The inability of microcirculatory vessels in SCD patients to recover to their baseline diameters between each stimulus could be partly linked to the magnitude of the decrease in NO bioavailability, which may vary over time, depending on the level of hemolysis. In addition, inflammation, which is chronically enhanced in SCD, could also cause dysfunction in sympathetic neurotransmitter regulatory mechanisms, particularly as a result of ageing.⁸ The combination of these factors may be found to modulate the sensitivity of microcirculatory vessels to external stimuli, resulting in various levels of vasoconstriction in SCD patients. The next step would be to study reflex vasoconstriction in larger cohorts of SCD patients and test the association with clinical severity, particularly the frequency of vaso-occlusive crises. Time to recovery of blood flow would be an interesting characteristic to be explored in the

future. Likewise, how this parameter evolves with time, with repeated lesions or with treatment, would be exciting research areas.

This study should also foster further work on the effects of novel strategies to improve treatment for patients with SCD. Drugs for SCD have targeted hemoglobin F upregulation, adhesion, or hemoglobin-oxygen affinity to decrease severe vaso-occlusive complications.⁹ Decreasing or stabilizing the extent of vasoconstriction could represent a new therapeutic field. For instance, it has been shown that SCD patients with depression or anxiety had more vaso-occlusive crises and episodes of acute chest syndrome than patients with better mental quality of life.¹⁰ Increasing the use of cognitive therapy and antidepressant treatment strategies to relieve anxiety may improve the high vasoconstrictive phenotype of SCD patients and limit the risk of complications.

Overall, the article by Veluswamy et al uncovers a neglected aspect of SCD pathophysiology and paves the way to therapeutic options directed at stabilizing vasomotor reactivity that may help reduce disease severity.

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TRANSPLANTATION

Comment on Chiesa et al, page 1201

HCT for CGD? Yes, and the sooner the better

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In this edition of *Blood*, Chiesa et al have described excellent outcomes after allogeneic hematopoietic cell transplantation (allo-HCT) for 712 patients with chronic granulomatous disease (CGD). This study reports the largest published cohort to date by a significant margin.¹

As a young hematologist set on becoming a transplant, I sought advice from someone more experienced than myself, and one of my colleagues replied, "Know as much as you can about the underlying disease. Understand the biology and

alternative therapeutic approaches. Constantly evaluate transplant outcomes. Don't just transplant because you can." Now, 25 years later and working in transplantation for rare immunodeficiencies, this approach is essential.

CGD is an inherited multisystem primary immunodeficiency characterized by life-threatening infections, immune dysregulation, and granulomatous inflammation. It is caused by genetic mutations encoding proteins of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, responsible for the generation of reactive oxygen species in phagocytes. Common disease manifestations include growth failure, skin and deep-seated abscesses, fungal pneumonia, lymphadenitis, inflammatory lung disease, and colitis.² With genetic mutations clearly restricted to the hematopoietic system, some may consider that proceeding to allo-HCT a "no brainer." Faced with a choice between potential cure or a slow decline in quality of life and reduced life expectancy, why has the role of transplantation been so fiercely debated?

CGD was first described in 1950. By the mid-1980s, very few affected individuals survived into adulthood, with a median life expectancy of 10 years. Management relied on antimicrobials and careful use of corticosteroids for inflammatory complications. The earliest attempts at curative allo-HCT in the late 1970s and 1980s were largely unsuccessful, with low rates of engraftment and unacceptably high transplant-related mortality. As a result, the majority of children with CGD continued to be treated conservatively, and with steady improvements in supportive care, most survived into adulthood.

Enthusiasm for allo-HCT was reignited in the early 2000s with the adoption of reduced toxicity conditioning regimens resulting in gradually increasing numbers of CGD patients undergoing allo-HCT across Europe, but fewer in the United States. In the last 5 to 10 years, the results of several transplantation series have been published, demonstrating excellent outcomes with overall survival (OS) rates in excess of 80%, a reduction in infection rates, and improvement in quality of life compared with pretransplantation condition.³⁻⁶ Simultaneously, clinical outcomes in adult CGD patients who did not receive a transplant have become available.^{6,7} They identify high rates of inflammatory complications and progressive decline in performance status, despite modern antimicrobial prophylaxis, biologics, and immunosuppressants. There is good evidence that clinical outcome is closely related to residual NADPH oxidase activity.⁸

The article by Chiesa and colleagues is significant because it reports on a large number of patients in multiple centers who received transplants with a variety of reduced-toxicity conditioning regimens; thus, it accurately reflects contemporary outcomes after allo-HCT. Notably, 87% of the transplantations were performed after 2006, the era in which effective antimicrobial and antifungal prophylaxis became available for conservatively managed patients. Their cohort included 77 adults and 635 children (younger than age 18 years at the time of transplant), with a median age at transplant of 7 years (range, 0.1-48.6 years) and a median follow-up of 45 months. Although the majority of transplants were performed in early childhood, the disease burden was high, with previous infections in 68%, chronic colitis in 24%, and liver or renal impairment in 14% of evaluable patients. These transplants were rarely preemptive. The 3-year OS was 85.7% for the whole cohort (Figure 1A in Chiesa et al). Predictably, the predominant causes of death were infection (42%) and graft-versus-host-disease (GVHD) (33%), with age ($P = .009$), pretransplant colitis ($P = .01$), and donor type ($P = .02$) having an influence on outcome on univariate analysis (Tables 2 and 3 in Chiesa et al). Multivariate analysis identified age and the use of a mismatched donor as statistically significant (Table 4 in Chiesa et al).

Most patients (75%) received in vivo T-cell depletion (TCD) in the form of antithymocyte globulin (ATG) or alemtuzumab. Donor engraftment was achieved in 88% of evaluable patients, with 12% suffering primary or secondary graft failure. Of the patients who went on to have a second procedure (for graft rejection or progressive fall in chimerism), the subsequent 3-year OS was 76.6%. As expected, overall GVHD rates were low, commensurate with TCD regimens (Figure 1G-H in Chiesa et al), with higher rates in the patients conditioned with regimens that contained busulfan-cytarabine compared with busulfan-fludarabine.

For CGD patients who reached adulthood without receiving a transplant (including those who were not offered a transplant in childhood, those who were symptomatic in childhood but diagnosed only as adults, or those with mild disease who presented for the first time as adults), this study provides further support for the

efficacy of allo-HCT. Several published transplantation series include adult patients,^{3,4,7,9} and although outcomes worsen with increasing age at transplantation, OS rates of >75% are observed along with a reduction in CGD-related complications.

As with other rare diseases, a timely prospective randomized controlled trial comparing allo-HCT with conservative therapy is not feasible, despite being highly desirable. The next best data arise from large retrospective analyses such as that provided in the study by Chiesa et al.

In 2020, CGD patients have a wide array of therapeutic options available to them, including modern antibacterial and antifungal agents, prophylactic interferon gamma, minimally invasive surgery, and/or interventional radiology for treatment of abscesses, monoclonal antibodies for colitis and inflammatory lung disease, allo-HCT and autologous gene therapy. Early reports suggest that gene therapy can offer the prospect of curative therapy without the risk of GVHD, although longer term follow-up is required.¹⁰

It has become clear that current approaches to allo-HCT are delivering excellent results for CGD patients of all ages and conservative management is improving, but there remain unanswered questions. What should we recommend for patients with mild symptoms and reasonably preserved NADPH oxidase activity? Although likely to do well in childhood, should these patients risk an early transplant-related death in order to prevent a progressive decline in quality of life as an adult and significantly reduced life expectancy? Which patients should be considered for gene therapy?

If you are asking me, transplant early. Inborn errors are for life, not just childhood. Adulthood with uncorrected CGD is all too often miserable.

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