Durable discontinuation of systemic therapy for chronic graft-*versus*-host disease: myth or reality?

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Progress in research into chronic graft-*versus*-host disease (GvHD) over last two decades has been impressive. Disease manifestations and clinical course are now well characterized, the complex pathophysiology is much better understood, many investigational agents are available for treatment, and a regulatory approval pathway has been established. The goals of the first National Institutes of Health consensus conference, held in 2005, have been achieved and we now have three Food and Drug Administration-approved novel agents for the treatment of chronic GvHD.[1] These new drugs hold promise of less toxicity, improved symptom control, and better patient function in steroid-refractory disease. Effective chronic GvHD prevention is now well established and the incidence of chronic GvHD can range as low as 10-12% with novel prophylactic regimens.[2,3] However, much work remains to be done. Initial treatment is still prednisone with or without a calcineurin inhibitor, which fails in about 50% of patients. Best choices of subsequent treatments are still being debated and even with novel drugs complete responses in these patients are still in the range of only 10%. Furthermore, highly morbid and disabling forms of chronic GvHD still exist.[4] We are still waiting to see published data on improved survival in patients with chronic GvHD and infections remain the leading cause of death in these patients.[5] The financial burden of the cost of therapy for chronic GvHD surpasses an average of $300,000/year per patient in the USA.[4] Taking all this together, it is no wonder that achieving sustained discontinuation of systemic therapy remains a highly desirable and still elusive goal in chronic GvHD. One of the major barriers is our current inability to reliably choose the tim-

Table 1. Studies evaluating time to permanent discontinuation of systemic therapy.

Author, year, reference	N	Definition off ST	% off ST	Setting	Risk factors for longer time to discontinuation
Chen 2022[6]	684	≥ 12 months	24% at 5 years 32% at 10 years	Multi-center	Peripheral blood Myeloablative conditioning Moderate-severe GI cGvHD Lee symptom score
Stewart 2004[7]	751	Not stated	50% at 7 years	Single center	Peripheral blood Female donor to male HLA mismatch Multiple cGVHD sites Elevated serum bilirubin
Perez 2008[8]	171	Not stated	68% at 5 years	Single center	Acute GvHD Moderate-severe GI cGvHD
Curtis 2017[9]	227	≥ 6 months	27.7% at 5 years	Qauternary center	Cyclosporine prophylaxis Extensive skin sclerosis
Lee 2018[10]	250	≥ 9 months	32% at 5 years	Single center	Shorter time from HCT Oral cGvHD Skin cGvHD

ST: systemic therapy; GI: gastrointestinal; cGvHD: chronic graft-*versus*-host disease; HCT: hematopoietic cell transplantation; GvHD: graft-*versus*-host disease.

ing and rate of tapering off systemic therapy, which results in endless cycles of trial-and-error treatments intertwined with disease flares and cumulative drug toxicities.

In this issue of *Haematologica*, Chen *et al.*[6] evaluate the factors associated with durable discontinuation of systemic therapy, defined rigorously as cessation of systemic therapy for at least 12 months, using data from two prospectively followed cohorts from the chronic GvHD consortium. The cumulative incidence estimate of durable discontinuation of systemic therapy was 24% and 32% at 5 and 10 years, respectively, after enrollment. Among patients who discontinued systemic therapy, the median time from chronic GvHD diagnosis to durable discontinuation of systemic therapy was 3.6 years. In multivariate analysis, several factors were identified as being associated with a lower likelihood of discontinuation of systemic therapy (Table 1). The authors also found that many factors known to be associated with the development of chronic GvHD were not associated with the likelihood of discontinuation of systemic therapy, suggesting that the pathophysiological mechanisms of chronic GvHD treatment and control may differ from those driving its initial development. These results suggest that a mandatory 6- to 12-month observation period is required to support the conclusion that systemic therapy has been discontinued permanently.

The applicability of the results of this study is limited by the population studied. Patients at low risk of developing chronic GvHD, such as young children or those who received post-transplant cyclophosphamide, antithymocyte globulin, or *in vivo/ex vivo* T-cell depletion for GvHD prophylaxis were not well represented. Previous studies of the discontinuation of systemic therapy reported rates as low as 27.7% and as high as 68% depending on the population under study and the rigor of the definition (Table 1). With newer GvHD prophylaxis regimens, a lower burden of systemic immunosuppression can be achieved, although the question of overall outcome superiority remains unanswered and drugs to provide a better balance of GvHD and graft-*versus*-leukemia effects are still needed.[2,3]

Systemic immunosuppressive therapy used to treat chronic GvHD can impair immunity, adding to the inherent immune dysfunction associated with active chronic GvHD, and therefore increase the risk of opportunistic infections and expose patients to the toxicity associated with the side effects of many medications. These side effects are of particular concern in the context of chronic glucocorticoid use, which has multiple systemic effects some of which can be irreversible, such as osteonecrosis, myopathy, growth failure in children, and osteopenia. There are three immunological scenarios that can unfold after infusion of allogeneic hematopoietic stem cells: (i) normal immunological reconstitution with the achievement of protective immunity and no GvHD – a state of genuine immunological tolerance in which the risk of leukemia relapse is also highest; (ii) so-called functional tolerance in which regulatory mechanisms are in effect resulting in no clinical GvHD, with good protection against relapse of the malignancy; and (iii) concurrent alloreactive proliferation and immune dysregulation, which are clinically reflected as acute and chronic GvHD and provide protection against malignancy relapse but at the expense of increased mortality, morbidity and long-term disability. This third scenario could be the most desirable one for cure of the malignancy if a way to mitigate GvHD along with eliminating other non-relapse related risks and side effects of therapy could be achieved. The latest 2020 National Institutes of Health chronic GvHD consensus proposed new strategies to achieve that goal.[4]

The paper by Chen *et al.*[6] challenges the central dogma plaguing the field of chronic GvHD for the last 40 years – the idea that patients need to be tapered off completely from systemic therapy in order to be declared successfully treated. While this seems to be possible in up to one-third of patients after 10 or more years of therapy, there is a large proportion of patients who need indefinite lines of systemic therapy or succumb to non-relapse mortality (most commonly infections). Chronic GvHD is an iatrogenic autoimmune disease but fundamentally not unlike other systemic autoimmune diseases known in medicine, which in their severe forms require lifelong systemic therapy for disease control. Furthermore, some of the drugs we tend to use most for chronic GvHD therapy, such as calcineurin inhibitors, corticosteroids and mycophenolate, are least likely to promote achievement of immunological tolerance and competence needed for normal immune reconstitution. It is said that the worst mistake is one that is being made repeatedly. It is likely that we need to abandon this paradigm that is now more than four decades old and accept that moderate-severe chronic GvHD is indeed “chronic” and to develop personalized and less toxic approaches instead of permanent “trial-and-error” strategies. To get to that point two things are urgently needed: (i) development of qualified biomarker-based immune profiles or algorithms for clinical use that will reliably indicate when chronic GvHD is controlled in an individual patient, so that adequate treatment doses can be given or tapering could be attempted, and (ii) biology-based therapies that allow the most personalized interventions, enabling chronic, successful treatment without detrimental toxicities or excess of malignancy relapses. Viewing chronic GvHD in this way has implications for management approaches and the development of new therapeutic agents. On the road to achieving this imperative goal, the paper by Chen *et al.* provides a long awaited wake-up call and a critical benchmark for future clinical trials.

Disclosures

No conflicts of interest to disclose.

Contributions

SP and KS co-wrote and edited the manuscript.

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