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Durable discontinuation of systemic therapy for chronic Graft-versus-Host Disease: myth or reality?

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Progress in chronic Graft-versus-Host Disease (GVHD) over last two decades has been impressive. Disease manifestations and clinical course are now well characterized, complex pathophysiology is much better understood, many investigational agents are available for treatment, and a regulatory approval pathway has been established. The 2005 first NIH consensus conference goals have been achieved and we now have three FDA 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. The effective chronic GVHD preventions are now well established and the incidence of chronic GVHD can range as low as 10-12% with novel prophylaxis 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%. Further, 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 leading cause of death in these patients.[5] Financial burden of the cost of therapy for chronic GVHD surpass an average of $300,000/year per patient in the U.S.[4] Taking this all together, it is no wonder that achieving sustained discontinuation of systemic therapy (ST) remains a highly desirable and still elusive goal in chronic GVHD. One of the major barriers is our current inability to reliably choose timing and rate of ST taper, 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] evaluated the factors associated with durable ST discontinuation defined rigorously as cessation of ST for at least 12 months, using data from two prospectively followed cohorts from the chronic GVHD consortium. The cumulative incidence estimate of durable ST discontinuation was 24% and 32% at 5 and 10 years, respectively, after enrollment. Among patients who discontinued ST, the median time from chronic GVHD diagnosis to durable ST discontinuation was 3.6 years. In multivariate analysis, several factors were identified to be associated with a lower likelihood of ST discontinuation (**Table**). Authors also found that many factors known to be associated with the development of chronic GVHD were not associated with the likelihood of ST discontinuation, 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 6-12 month observation period is required to support the conclusion that ST has been discontinued permanently. Applicability of this study is limited by the population studied. Patients at low risk for developing chronic GVHD, such as young children or those who received post-transplant cyclophosphamide, ATG, or *in vivo / ex vivo* T cell depletion for GVHD prophylaxis are not well represented. Previous studies of ST discontinuation 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**). With newer GVHD prophylaxis regimens, a lower burden of systemic immunosuppression can be achieved, though the question of overall outcome superiority remains uncertain and drugs to provide better balance of GVHD/GVL effects are still needed.[2,3]

Systemic immunosuppression therapy used to treat chronic GVHD can impair immunologic function in addition 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 many medications side effects. 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: a) normal immunological reconstitution with the achievement of protective immunity and no GVHD – a state of genuine immunological tolerance where also the highest risk of leukemia relapse may exist; b) so-called functional tolerance where regulatory mechanisms are in effect resulting in no clinical GVHD, with good protection against malignancy relapse; and c) 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 pathway for malignancy cure 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 NIH chronic GVHD consensus proposed new strategies to achieve that goal.[4]

This paper by Chen et al[6] challenges the central dogma plaguing the field of chronic GVHD for the last forty years – the idea that patients need to be tapered off completely

from ST to be declared a success. 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 ST 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 its severe forms require lifelong ST for disease control. Furthermore, some of the drugs we tend to most use for chronic GVHD therapy such as calcineurin inhibitors, corticosteroids or mycophenolate are least likely to promote achievement of immunological tolerance and competence needed for normal immune reconstitution. It is said that worst mistake is one that is being repeatedly made. It is likely that we need to abandon this more than four decades old paradigm 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 will be urgently needed: 1) 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 doses can be given or tapering could be attempted, and 2) biologically-based treatments that allow the most personalized intervention that will allow chronic and 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 of achieving this imperative goal, the current paper by Chen et al provides a long awaited wake-up call and a critical benchmark for future clinical trials.

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Table. 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 mo	24% at 5 yrs 32% at 10 yrs	Multi-center	Peripheral blood Myeloablative conditioning Mod-severe GI cGVHD Lee symptom score
Stewart 2004[7]	751	Not stated	50% at 7 yrs	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 yrs	Single center	Acute GVHD Mod-severe cGVHD
Curtis 2017[9]	227	≥ 6 mo	27.7% at 5 yrs	Quarterly center	Cyclosporine prophylaxis Extensive skin sclerosis
Lee 2018[10]	250	≥ 9 mo	32% at 5 yrs	Single center	Shorter time from HCT Oral cGVHD Skin cGVHD