blood advances

Steroid tapering after GVHD Rx: not too fast, not too slow

Paul J. Martin

Division of Clinical Research, Fred Hutchinson Cancer Center and Department of Medicine, University of Washington, Seattle, WA

Comment on Akahoshi et al, page 2047

In this issue of *Blood Advances*, Akahoshi et al[1] provided evidence that higher serum concentrations of suppression of tumorigenicity 2 (ST2) and regenerating family member 3 alpha (REG3α) at the onset of complete or nearly complete response (CR) after initial systemic treatment of acute graft-versus-host disease (GVHD) indicate clinically silent persistence of GVHD activity. Measurement of these biomarkers could help determine whether tapering of immunosuppressive treatment should continue or not.

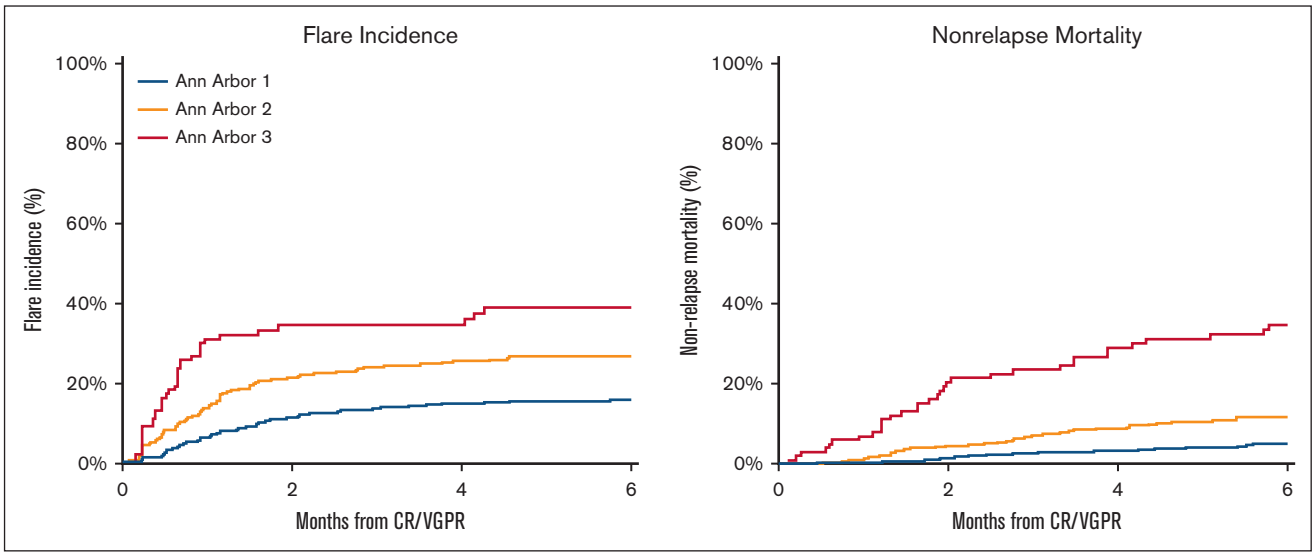
Clinicians use prednisone or methylprednisolone (MP) at doses of 0.5 to 2.0 mg/kg per day for the initial treatment of acute GVHD. The tapering of corticosteroid doses begins gradually at the initial onset of response, and the rate of tapering depends on the rate of improvement, balanced by treatment-related side effects. After CR or a very good partial response (VGPR), the absence of clinical manifestations of GVHD makes it more difficult to balance the risks and benefits when deciding how quickly to taper corticosteroid dosing. Tapering too slowly causes treatment-related toxicity, whereas tapering too rapidly increases the risk of GVHD flares and the associated higher risk of nonrelapse mortality (NRM).

Akahoshi et al[1] measured serum concentrations of ST2 and Reg3α at the onset of CR/VGPR after initial treatment for acute GVHD and used a prespecified 3-tier categorical algorithm to evaluate associations with the subsequent risks of flare and NRM. Flare after response was defined as worsening of GVHD by at least 1 stage in any organ managed by increasing the MP-equivalent corticosteroid dose by at least 0.25 mg/kg per day or by adding another systemic agent.

In the analysis, 3 independent risk factors stood out for having strong associations with a higher risk of flares after CR/VGPR: higher ST2/Reg3α concentrations (see figure, left), earlier response in the subset of patients who had low ST2/Reg3α concentrations at CR/VGPR, and a faster corticosteroid taper rate after CR/VGPR. Two GVHD-related risk factors stood out for having strong associations with a higher risk of NRM after CR/VGPR: higher ST2/Reg3α concentrations at CR/VGPR (see figure, right) and subsequent flare.

The positive association between faster corticosteroid tapering and the risk of flare was stronger in patients with intermediate and high biomarker values than in those with low biomarker values, suggesting that slower tapering could decrease the risk of flares. However, the association between higher biomarker values and the risk of flares was not attenuated by including the corticosteroid taper rate in the multivariable model, suggesting that to have an optimal effect on the risk of flares, taper rates might have to be slower than those used in current practice.

Although the authors have shown that 3-tier and 2-tier ST2/Reg3a categorical algorithms predict GVHD-related outcomes after hematopoietic cell transplantation,[2-6] no studies have yet shown that the use of these biomarkers can improve outcomes for patients. Two internally controlled open-label phase 2 studies examined whether low-risk acute GVHD, defined in part by ST2/Reg3α concentrations, could be successfully managed without corticosteroid treatment. The BMT CTN 1501 trial compared sirolimus alone and prednisone at 2 mg/kg per day in patients with Minnesota standard-risk GVHD and low- or intermediate-risk ST2/Reg3α biomarker values.[7] Another trial compared itacitinib alone and prednisone at ~1 mg/kg in patients with Minnesota standard-risk GVHD and low-risk biomarker values.[8] Neither study showed any statistically significant difference in the primary end point of the day 28 response or NRM between the arms. The incidence of hyperglycemia was lower in the sirolimus arm of the BMT CTN 1501 study, and the incidence of serious infections was lower in the itacitinib arm of the second study. Similarly, a single-arm phase 2 study with matched external controls showed no



Prediction of outcomes after treatment of acute GVHD. Ann Arbor 1 (low), 2 (intermediate), and 3 (high) ST2/Reg3α biomarker risk scores at the onset of complete or nearly complete resolution of acute GVHD after systemic treatment predict the subsequent risks of disease flare (left) and NRM (right) as corticosteroid dosing is tapered. Figure adapted from Akahoshi et al.[1]

statistically significant improvement in outcomes when natalizumab was added to corticosteroids compared with corticosteroids alone for the initial treatment of acute GVHD with intermediate and high-risk ST2/Reg3α biomarker values.[9]

The results reported by Akahoshi et al[1] raise the question of whether ST2/Reg3α concentrations could assist in clinical decision-making not for groups of patients, as in the clinical trials discussed above, but for individual patients. This question could (and in my view, should) be tested in a large randomized pragmatic trial in which biomarker testing would be performed with results disclosed to half of the participants at the onset of CR/VGPR, leaving providers and patients free to use the results at their discretion with guidance from the protocol. The other half of the participants would have samples drawn at the onset of CR/VGPR, with biomarker testing deferred to the end of the study. This study would test the hypothesis that the incidence of subsequent flares and NRM is lower among participants who had corticosteroid tapering informed by biomarker test results than among controls who did not, with the analysis adjusted according to biomarker concentrations at the onset of CR/VGPR. The results in the control arm would also serve as an opportunity to validate the results of the current study, an important goal because the current study excluded patients with GVHD that did not reach CR/VGPR within 28 days after starting treatment and because samples were not available from ~25% of the patients who were otherwise eligible.

Although the biomarker algorithm used by Akahoshi et al[1] was originally developed to predict survival from day 7 after transplantation,[2] it has good predictive ability to discriminate outcomes after treatment for acute GVHD. Nonetheless, its 3-tier categorical structure limits its utility for application to individual patients. For this purpose, it would be of enormous interest to determine whether biomarker and corticosteroid taper data from the current study could be used together to predict the probability of flare in a calibrated way, as explored, for example, with the use of clinical biomarkers to predict the risk of mortality after second-line treatment of acute GVHD.[10] By measuring the severity of clinically silent GVHD activity at the onset of CR/VGPR after initial treatment for acute GVHD, a calibrated and validated predictive algorithm that incorporates biomarker values and corticosteroid taper rates would enable clinicians to adjust the corticosteroid taper rate in a fully informed manner that balances the benefits of continued disease control vs the toxicity of continued corticosteroid treatment.

Conflict-of-interest disclosure: P.J.M. declares no competing financial interests.

References

1. Akahoshi Y, Spyrou N, Hoepting M, et al. Flares of acute graft-versus-host disease (GVHD): a Mount Sinai Acute GVHD International Consortium (MAGIC) analysis. *Blood Adv*. 2024;8(8):2047-2057.
2. Hartwell MJ, Özbek U, Holler E, et al. An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. *JCI Insight*. 2017;2(3):e89798.
3. Major-Monfried H, Renteria AS, Pawarode A, et al. MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. *Blood*. 2018;131(25):2846-2855.
4. Srinagesh HK, Özbek U, Kapoor U, et al. The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease. *Blood Adv*. 2019;3(23):4034-4042.
5. Etra A, Gergoudis S, Morales G, et al. Assessment of systemic and gastrointestinal tissue damage biomarkers for GVHD risk stratification. *Blood Adv*. 2022;6(12):3707-3715.
6. Spyrou N, Akahoshi Y, Ayuk F, et al. The utility of biomarkers in acute GVHD prognostication. *Blood Adv*. 2023;7(17):5152-5155.

7. Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood*. 2020;135(2):97-107.
8. Etra A, Capellini A, Alousi A, et al. Effective treatment of low-risk acute GVHD with itacitinib monotherapy. *Blood*. 2023;141(5):481-489.
9. Al Malki MM, London K, Baez J, et al. Phase 2 study of natalizumab plus standard corticosteroid treatment for high-risk acute graft-versus-host disease. *Blood Adv*. 2023;7(17):5189-5198.
10. Vo P, Gooley TA, Carpenter PA, et al. Prediction of outcomes after second-line treatment for acute graft-versus-host disease. *Blood Adv*. 2022;6(11):3220-3229.

https://doi.org/10.1182/bloodadvances.2024012850