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Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness

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Graft-versus-host disease (GVHD) remains a major limitation of allogeneic hematopoietic stem cell transplantation. Only half of patients with severe acute GVHD respond to first-line treatment with corticosteroids and, for several decades, there was no optimal second-line treatment of patients with corticosteroid-refractory acute GVHD. Ruxolitinib was recently approved for the treatment of corticosteroid-refractory acute GVHD in adult and pediatric patients 12 years and older. Thus, it is important to define the patient population that would now be considered as refractory to ruxolitinib vs ruxolitinib dependent. Here, we propose to define ruxolitinib-refractory acute GVHD as disease that shows: (1) progression of GVHD compared with baseline after at least 5 to 10 days of treatment with ruxolitinib, based either on objective increase in stage/grade, or new organ involvement; (2) lack of improvement in GVHD (partial response or better) compared with baseline after ≥14 days of treatment with ruxolitinib; or (3) loss of response, defined as objective worsening of GVHD determined by increase in stage, grade, or new organ involvement at any time after initial improvement. GVHD manifestations that persist without improvement in patients who had a grade ≥3 treatment-emergent and ruxolitinib-attributed adverse event that did not resolve within 7 days of discontinuing ruxolitinib would serve as a clinical indication for additional treatment. In addition, absence of complete response or very good partial response at day 28 after ruxolitinib could be considered as an eligibility criterion. (*Blood*. 2020;136(17):1903-1906)

Introduction

The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) continues to rapidly increase worldwide.[1] However, graft-versus-host disease (GVHD) remains a major limitation of a successful allo-HSCT.[2,3] Up to 50% of patients will develop acute GVHD, despite immunosuppressive prophylaxis,[3-5] and this complication is a significant cause of mortality in these patients.[6-9] Only half of patients with acute GVHD respond to first-line treatment with corticosteroids.[9,10] For several decades, there was no optimal second-line treatment of corticosteroid-refractory acute GVHD.[11] A major limitation of many studies investigating salvage therapies for corticosteroid-refractory acute GVHD is the heterogeneous definition of "refractory," which may preclude an accurate comparison across studies.

Nevertheless, and despite some differences, some agreement has been reached in defining corticosteroid-refractory acute GVHD as disease (1) progression after 3 days of treatment with methylprednisolone (MP) 2 mg/kg per day equivalent, (2) did not improve after 7 days of treatment with MP 2 mg/kg per day equivalent, (3) progressed to a new organ after treatment with MP 1 mg/kg per day equivalent for skin and upper gastrointestinal GVHD, or (4) recurred during or after a corticosteroid taper (Table 1).[12] Such pragmatic criteria are mainly intended to ensure that participants in clinical trials have an unequivocal diagnosis of corticosteroid-refractory GVHD.

From a practical standpoint, a "recurrent" GVHD implies that GVHD resolved at some point during treatment. However, the most common scenario is an exacerbation or flare of a GVHD that had shown some evidence of improvement before corticosteroid doses were tapered. In this context, the taper rate is extremely important, because a sudden decrease of the MP dosage from 2 mg/kg per day to 1 mg/kg per day is frequently accompanied by exacerbation of GVHD manifestations. Therefore, this criterion is applicable only when steroid doses are tapered progressively at an appropriate rate. In addition, this criterion should specify ideally some upper limit of the corticosteroid dose, because the risks of continued treatment with MP at dosages lower than 0.4 mg/kg per day might not justify the risks and uncertainties of a new investigational treatment if GVHD is improving, however slowly. For example, exacerbation of GVHD manifestations that occur when the prednisone dose is tapered to 0.2 mg/kg could be managed simply by increasing

Table 1. Criteria for corticosteroid-refractory and ruxolitinib-refractory acute GVHD

Criteria
Corticosteroid-refractory acute GVHD (1) Disease progression after 3 days of treatment with MP 2 mg/kg per day equivalent, (2) Lack of improvement after 7 d of treatment with MP 2 mg/kg per day equivalent, (3) Progression to a new organ after treatment with MP 1 mg/kg per day equivalent for skin and upper gastrointestinal GVHD, or (4) Recurrence during or after a corticosteroid taper.
Ruxolitinib-refractory acute GVHD (1) Progression of GVHD compared with baseline after ≥5 to 10 days of treatment with ruxolitinib, based either on objective increase in stage/grade or new organ involvement; (2) Lack of improvement in GVHD (PR or better) compared with baseline after at least 14 days of treatment with ruxolitinib; or (3) Loss of response, defined as objective worsening of GVHD determined by increase in stage, grade or new organ involvement at any time after initial improvement.

the prednisone dose by 1 or 2 steps in the taper schedule and resuming the taper when GVHD manifestations begin to improve again.

Beyond clinical trials, routine management of corticosteroid-refractory acute GVHD is very complex and requires careful consideration of the anticipated benefits and risks of continuing current treatment vs changing it or adding a new treatment. These considerations include the severity of GVHD, the trajectory of recent changes in clinical manifestations, and whether the current treatments have been given for enough time to predict the future evolution of the disease with confidence. The tolerability of therapy adds another level of complexity that should consider the trajectory and reversibility of adverse effects caused by the current treatment(s). Obviously, clinicians will have to make decisions in the face of uncertainty about the level of confidence that any given change of treatment will improve the clinical manifestations or reduce the side effects.[13]

Ruxolitinib for corticosteroid-refractory acute GVHD

Ruxolitinib was approved in May 2019 in the United States for the treatment of corticosteroid-refractory acute GVHD in adult and pediatric patients 12 years and older.[14] This approval was based on an open-label, single-arm, multicenter study (called REACH1) of ruxolitinib, which enrolled patients with corticosteroid-refractory acute GVHD grades 2 to 4 (Mount Sinai Acute GVHD International Consortium criteria).[15] The trial's primary end point was day-28 overall response rate (ORR), defined as complete response (CR), very good partial response (VGPR), or partial response (PR) by the Center for International Blood and Marrow Transplant Research criteria. A key secondary end point was duration of response at 6 months. In all, 71 patients received ≥1 dose of ruxolitinib. At day 28, 39 patients (55%) had an ORR, including 19 (27%) with CR. The median duration of response was 345 days. The overall survival (OS) estimate at 6 months was 51%. Of note, the median duration of ruxolitinib treatment of all patients was 46 (range, 4-473) days.

The more recent REACH2 phase 3 randomized trial investigating ruxolitinib vs best-available therapy in patients with corticosteroid-refractory acute GVHD has further established the role of ruxolitinib in the treatment of corticosteroid-refractory acute GVHD. The ORR at day 28 was higher in the ruxolitinib group than in the control group (62% vs 39%; odds ratio, 2.64; 95% confidence interval [CI], 1.65-4.22; $P < .001$). Similarly, the durable ORR at day 56 was higher in the ruxolitinib than in the control group (40% vs 22%; odds ratio, 2.38; 95% CI, 1.43-3.94; $P < .001$).[16]

Defining ruxolitinib-refractory acute GVHD

With the advent of ruxolitinib as a new second-line standard salvage therapy for corticosteroid-refractory acute GVHD, it is becoming increasingly important to define the patient population that would now be considered as refractory to ruxolitinib vs ruxolitinib dependent. We developed a proposal based on the available clinical evidence to define ruxolitinib-refractory acute GVHD. In the REACH1 and REACH2 trials, 45% and 38% of patients did not have a CR or PR at day 28, respectively. Moreover, in the REACH2 trial, the ORR at day 56 after initiation of therapy decreased to 40%, suggesting a clear unmet medical need for patients with GVHD who did not respond at day 28 or worsened afterward. Here, we discuss the eligibility criteria for third-line treatment trials enrolling patients who received second-line treatment with ruxolitinib.

In the REACH1 trial, the median time to initial response was 7 days (range, 6-49 days), and 61% had an initial response within 14 days.[15] Additional information comes from 3 retrospective studies showing that the median time to initial response after starting ruxolitinib for treatment of steroid-refractory acute GVHD ranged from 10 to 14 days.[17-19] Times to initial response attributable to ruxolitinib (ie, before changing or adding new treatment) in these studies ranged from 7 to 77 days[17] to 2 to 65 days[18] to 3.5 to 28 days.[19] Altogether, these data suggest that in most patients, improvement occurs within 14 days after starting treatment with ruxolitinib, although initial responses have been observed much later in some patients. The minimum duration of treatment with ruxolitinib was 4 days in the REACH1 trial,[15] 6 days in the REACH2 trial,[16] and 11 days in the retrospective study by Abedin et al.[20] Finally, a worldwide social media survey of 184 hematologists and transplant physicians showed that 13% would consider alternative treatment as early as 7 days after starting ruxolitinib in patients with no improvement, while 12% would wait until at least 10 days, 40% would wait until at least 14 days, and 35% indicated that they would wait until at least 21 days (M.M., unpublished data).

We propose that trials for patients with GVHD that has not responded adequately to ruxolitinib could have the following eligibility criteria: (1) progression of GVHD compared with baseline after at least 5 to 10 days of treatment with ruxolitinib, based either on objective increase in stage/grade, or new organ involvement; (2) lack of improvement in GVHD (PR or better) compared with baseline after at least 14 days of treatment with ruxolitinib; or (3) loss of response, defined as objective worsening of GVHD determined by increase in stage, grade, or new organ involvement at any time after initial improvement (Table 1). GVHD manifestations that persist without improvement in patients who had grade ≥3 treatment-emergent and ruxolitinib-attributed adverse event that did not resolve within 7 days of discontinuing ruxolitinib would serve as a clinical indication for additional treatment, but the GVHD in such a case could not be defined as resistant or refractory to treatment with ruxolitinib. In addition, absence of CR or VGPR[21]

at day 28 after ruxolitinib could be considered as an eligibility criterion, based on historical observations that outcomes in patients with PR that does not meet criteria for VGPR are similar to those in patients without CR or PR at day 28.[22] Further analysis of results from the REACH1 and REACH2 trials will be needed to determine whether this observation hold true for patients treated with ruxolitinib. Patients with GVHD that recurs when doses of ruxolitinib are tapered at the end of treatment may have ruxolitinib-dependent GVHD, which would be managed most appropriately by continued treatment with ruxolitinib, because unlike corticosteroid treatment, long-term treatment with ruxolitinib is usually well tolerated.[15,16]

Discussion

Any staging and grading scale of acute GVHD has some arbitrary boundaries. In routine practice, a slight change of the daily stool volume or skin involvement would not necessarily mean that acute GVHD severity is worse even if the overall acute GVHD grade has increased. From a practical standpoint, the trajectory of worsening or improvement should be judged according to smaller increments of change per unit time on a continuous scale and by qualitative changes (eg, intensity of erythema). Worsening of rash, diarrhea, or liver function from one day to the next should prompt concern even if the overall acute GVHD grade has not changed, and other causes should be excluded before attributing changes to GVHD. Despite these limitations, we believe that the above pragmatic definition of ruxolitinib-refractory acute GVHD would not only allow physicians to refine the decision-making process for treating such patients but also guide and harmonize the development of novel therapies in this subgroup of patients with highly unmet medical need, because uncertainty of outcomes in a clinical trial requires a very conservative and unambiguous approach in defining eligibility. Once the trial results have informed the assessment of the balance of benefits and risks, the definition of the clinical indication can be adjusted accordingly, in many cases to relax the criteria but, in some cases, to make them more stringent.

Beyond clinical trials, these criteria could be further refined by drawing a distinction between gut involvement and skin or liver involvement regarding lack of improvement after at least 7 days. For skin and liver involvement, one might reasonably expect that an effective treatment would produce measurable improvement within 7 days, even if the improvement did not decrease an organ stage. For example, a rash could begin to fade, but the extent of rash body surface might not. Similarly, the serum bilirubin concentration might show a change of trajectory without decreasing the organ stage. A short-term criterion (eg, 7 days) might not apply for the gastrointestinal involvement, because improvement in stool volume requires epithelial repair. In addition, evaluation of stool volume should account for oral intake. Improvement of intestinal GVHD is best demonstrated by decreased stool volume with increased ability to tolerate a normal diet. Therefore, and with the above limitations, waiting for a full 14 days before modifying therapy would be a reasonable general approach, before concluding that the probability of future improvement is so low that the risks and uncertainties of a new investigational treatment are justified. The need to wait at least 14 days would be obviated in settings where biomarkers are available to predict poor outcomes accurately when measured at earlier time points after starting treatment.[23]

Application of the MAGIC biomarker (ST2 and REG3α) algorithm evaluated at day 7 after systemic treatment of GVHD consistently separated steroid-resistant patients into 2 groups with dramatically different nonrelapse mortality and OS. Future studies should evaluate whether high biomarker levels at day 7 after treatment with ruxolitinib predict day 28 response or subsequent nonrelapse mortality and OS. We view the proposed definition of ruxolitinib-refractory acute GVHD as provisional, and we encourage consideration within scientific societies (eg, European Society for Blood and Marrow Transplant, American Society for Transplantation and Cellular Therapy, or Center for International Blood and Marrow Transplant Research) or working groups, such as the MAGIC consortium. Beyond defining ruxolitinib-refractory acute GVHD, a further question in this debate is whether new investigational agents should continue to be tested as second-line treatment (reviewed by Malard et al[11]) now that ruxolitinib has been approved for this indication. The results with ruxolitinib are quite impressive, but considerable room for improvement remains. At this stage, it is difficult to draw a final conclusion as to whether the development pathway for a new product has to proceed sequentially from third-line to second-line to first-line treatment. The answer will depend on a careful balancing of the anticipated immediate benefits and risks of a new agent and on consideration of future options if no immediate benefit is realized. Eligibility criteria for efficacy trials should aim to avoid enrolling patients who are likely to fare better with an alternative treatment on the one hand and similarly avoid enrolling patients who cannot benefit because GVHD has likely become irreversible on the other hand. Investigators should give careful consideration along the above lines in defining eligibility in clinical trials, because one size has rarely fit all in the treatment of severe acute GVHD.

Authorship

Contribution: M.M. performed the bibliographic search and wrote the first version of the manuscript; and all authors contributed to design and writing, editing, and revising this manuscript.

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Footnote

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