

Patient-reported treatment response in chronic graft-versus-host disease

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Treatment response in chronic graft-versus-host disease (cGvHD) is assessed using National Institutes of Health (NIH) Consensus criteria in clinical studies and by clinician assessment in routine practice. The paper by Im *et al.* in this issue of *Haematologica* provides new insight into 6-month patient-reported treatment response in cGvHD that was associated with subsequent failure-free survival (FFS) but had limited correlation with NIH and clinician-assessed response.¹

So far, patient-reported outcomes (PRO) have been mainly investigated to examine the association of cGvHD symptoms with quality-of-life (QoL), revealing poor functional status, inability to return to work, disrupted activities of daily living, and increased symptom burden.² In a natural history study, cGvHD severity was negatively associated with nearly all functional and QoL outcome measures, including the Lee Chronic GVHD Symptom Scale (LSS), Medical Outcomes Study Short Form-36-item questionnaire (SF-36), Physical Component Scale, 2-minute walk, grip strength, range of motion, and Human Activity Profile (HAP).³ Joint/fascia, skin, and lung involvement affected function and QoL most significantly, and showed the greatest correlation with outcome measures. Of note, physicians generally underestimated changes in patients' QoL.⁴

In the paper by Im *et al.* on 382 cGvHD patients of two prospective studies, PRO were investigated to assess whether patient-reported response measures may capture clinical benefit differently from standard NIH or clinician-reported response measures.¹ Physicians and patients rated overall changes in cGvHD manifestations with an 8-point scale,⁵ and in addition, patients completed the SF-36 and the LSS. At six months, 270 (71%) patients reported cGvHD improvement defined as: completely gone, very much better, moderately better, or a little better. PRO had limited correlation with either clinician-reported or NIH cGvHD response criteria.⁵ Per NIH response, only 46% of patients had improvement whereas clinicians reported 66% improvement in cGvHD at six months. In multivariable

analysis of PRO results, moderate-severe lung involvement at enrollment was associated with no improvement, whereas NIH-defined responses in eye, mouth and lung were associated with patients' report of improvement at six months. In addition, improvement from enrollment to six months in the LSS eye score was significantly associated with patients' report of improvement. Thus, investigating tools that capture symptom burden allow better insight into improvements in patients' perception of cGvHD and their QoL. Importantly, PRO at six months were significantly associated with subsequent FFS that was primarily driven by changes in immunosuppressive therapies, offering a good demonstration that, in the real world, continuation or change of cGvHD-specific treatments is based on clinicians' response assessment combined with patients' information on QoL, changes in symptom burden, and function. This clinical routine is in contrast to the treatment response assessment requested in clinical trials where clinician-assessed and patient-reported signs and symptoms, LSS, and the clinician-assessed and patient-reported global rating scales have been used as cGvHD-specific core measures.^{5,6} The fact that PRO had limited correlation with NIH cGvHD response criteria, and that per NIH response only 46% compared to 71% of patients in self-reports had cGvHD improvement after six months in the present study is worrisome since an NIH-defined non-responder would not meet the primary efficacy endpoint in treatment studies. The increasing importance of PRO is also reflected in the US Food and Drug Administration approval of ibrutinib for treatment of patients with refractory cGvHD since it is plausible that clinician-documented measures and results of the LSS were correlated with clinical responses.⁶

Recently, Lee *et al.* reported a strong correlation between clinical response measures and clinically meaningful changes in LSS in cGvHD patients treated with belumosudil.⁷ They observed an excellent correlation of improvements of skin, mouth, eye, upper gastrointestinal (GI) tract, and lung, supporting the use of PRO for response assess-

ment in cGvHD clinical trials and patient care to capture the patients' perspective on cGvHD disease activity. However, there was a poor correlation between clinical and PRO responses in joints, esophagus, lower GI tract, and pulmonary function tests. The discrepancy in the findings in the paper of Im *et al.* demonstrate quite well that the selection of PRO tools can possibly have an impact on results and that there remains an urgent need to validate PRO measures besides the LSS, as recently suggested in a systematic review of 64 articles reporting on 27 PRO.⁸ In this review, only HAP, LSS and the NIH Eleven Point Scale had evidence to support strong reliability, responsiveness, and validity within the cGvHD population.

In the study by Im *et al.*, 6-month patient-reported response was associated with subsequent FFS but did not significantly impact overall survival (OS).¹ Improved FFS is an important outcome for patients with cGvHD since treatment failure resulting in the need of additional lines of immunosuppressive therapies can substantially increase patients' risk of severe infectious complications and organ toxicity. There has been little agreement between the results on treatment response and outcome of patients with cGvHD published so far. In a prospective observational trial on 575 cGvHD patients, 6-month clinician-reported response and 2014 NIH-calculated response significantly correlated with subsequent FFS.⁹ In addition, a change in the 2005 NIH 0 to 3 clinician-reported skin score and 0 to 10 patient-reported itching score predicted subsequent

FFS, whereas change in the LSS predicted subsequent OS and non-relapse-mortality. In a multicenter prospective cohort of 283 cGvHD patients, a correlation between overall and organ-specific responses at six months with the corresponding overall and organ-specific changes in patient-reported symptom burden using multiple PRO was observed.¹⁰ However, overall response at six months did not correlate with changes in QoL measures or with OS.

PRO measures are a valuable tool for monitoring disease progression and treatment response, and are likely to provide benefit in GvHD clinical practice and research. So far, patient-reported QoL measures have served as secondary endpoints but were not considered in primary study endpoints since these only included quantitative measures of cGvHD activity. Therefore, an area for future investigation would be to determine methods to integrate objective and subjective measures into holistic assessments of cGvHD disease activity and how this changes under immunosuppressive/immunomodulatory therapy. This should take place in cGvHD clinical trials, drug development, and routine clinical practice to objectively document, as well as possible, improvements in cGvHD manifestations, as well as symptom relief and patients' clinical benefit.

Disclosures

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