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Graft versus host disease clinical trials: Is it time for patients centered outcomes to be the primary objective?

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Abstract

Purpose of review: Graft versus host disease (GVHD) is a common complication following Hematopoietic Cell Transplant, and is associated with a high symptom burden, reduced functional status and impaired quality of life (QOL). QOL is best assessed by Patient-Reported Outcomes (PRO). Numerous clinical trials for prevention and treatment of GVHD are available. This review aims to understand the landscape of PRO inclusion in clinical trials for GVHD over the last decade.

Recent findings: Consensus bodies, including experts in GVHD, PRO and clinical trials have made recommendations for a standardized approach for the inclusion of PRO in clinical trials including as primary outcomes, however, these have yet to be implemented in a consistent manner in practice.

Summary: Consistently applying consensus recommendation in chronic GVHD will ensure PROs are appropriately included in clinical trials. Development of validated measures in acute GVHD and composite outcomes for all GVHD trials are required.

Keywords

Hematopoietic cell transplantation; Graft versus Host Disease; Patient-reported outcomes; Clinical trials

Introduction

The field of Hematopoietic Cell Transplantation (HCT) is increasingly embracing a patient-centered approach to care including the collection and assessment of Patient-reported Outcomes (PRO), subjective reports directly from the patient, describing their symptom burden, functional status and overall quality of life (QOL). PROs are beginning to be incorporated into both clinical care and research, but their use is currently not standardized, whether considering the measures to use, the time points for collection, the mode of

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Conflict of Interest

Bronwen E Shaw declares that he has no conflict of interests.

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collection and the interpretation and action which should result from the PRO scores. Likewise their use in clinical trials frequently remains unstandardized and often PRO endpoints are not treated with the same rigor as other endpoints in the protocol (1).

Graft versus Host Disease (GVHD) is a very common complication following HCT, with numerous clinical trials addressing the use of novel agents or strategies for both prevention and treatment. Acute GVHD (aGVHD) predominant affects the skin, liver and GI tract and may be associated with very troublesome symptoms, physician report of some of which form the basis for grading and staging. Chronic GVHD (cGVHD) is a multisystem disease associated with an increased symptom burden, reduced functional status and impaired QOL with increased mortality. Given this profile, GVHD is a disease where the patient's perspective is critical.

The aim of this review is to summarize the landscape of PRO inclusion in clinical trials in GVHD over the last decade, addressing 1. clinical trials that are currently ongoing or recently completed, 2. consensus statements by expert groups in GVHD, and 3. advances in PROs outside of GVHD but relevant to clinical trials, HCT and GVHD.

PROs in GVHD clinical trials: position in late 1990s/early 2000s

In 2009, Lee et al published a consensus document reporting on discussion by several interested groups (including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Center for International Blood and Marrow Transplantation Research (CIBMTR) and American Society for Blood and Marrow Transplantation (ASBMT)) on the role of PROs in trial design and interpretation for aGVHD prevention and treatment trials (2). They concluded that GVHD prophylaxis studies are unlikely to benefit from PRO collection as the current agents to prevent GVHD are relatively ineffective, result in small changes in GVHD rates and that these agents are given at the time early post-HCT when patients have many symptoms related to multiple causes (2). For treatment trials in aGVHD designing a measure and collecting PROs is challenging due to several factors including, the need for frequent measures at a time when patients may be very unwell, certain characteristics of GVHD (e.g. liver involvement) not resulting in symptoms, and many other post-HCT factors contributing to symptoms at this time (2). Nevertheless, the authors conclude that there is an urgent need for a validated instrument that meets the requirement for a FDA claim approval for use in aGVHD treatment trials. In cGVHD, the 2006 NIH Design of Clinical Trials Working Group report recommended the inclusion of PROs in cGVHD clinical trials as secondary outcomes. Although the value of PROs is noted, they state that PROs are subject to problems of bias and missing data, may lack specificity and that few measures show evidence of sensitivity to change. No specific PRO measures were proposed. They call for development of pediatric measures (3).

FDA guidance on the requirements for a PRO instrument to be considered adequate as an endpoint, at least in clinical trials for medicinal product labeling, was published in 2009 (4). This includes a requirement for careful consideration of the role of the endpoint in each trial, the need for the PRO instrument to be valid and reliable, including in the specific target

patient population and that the PRO outcome be supported by an objective clinical measure of drug activity (4, 5).

Current or recent GVHD clinical trials

A search of clinicaltrials.gov using the term 'Graft Versus Host Disease' reveals 457 studies (October 2018). Incorporating either 'Patient-Reported Outcomes' or 'Quality of Life' identifies 8 and 37 trials respectively. After accounting for duplicates (n=2), withdrawn/unknown status (n=3), not clinical trial (n=5), outcomes not GVHD-specific (n=4), QOL/PRO not outcome (n=2); a total of 29 studies remain. These can be divided broadly into the category of prophylaxis/prevention studies (n=4, table 1), GVHD treatments studies in the recruitment phase (n=9, table 2) and GVHD treatments studies which have completed (n=16, table 3). PRO measures, where available on clinicaltrials.gov, are included in the tables. Studies include between one and five measures. There are seven aGVHD treatment trials, using the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) (6) (n=2), MD Anderson Symptom Inventory (MDASI) (7) (n=2), Short-form-36 (SF36) (8) (n=1) and the EQ-5D (9) (n=1). In the 18 cGVHD treatment trials, the Lee cGVHD Symptom Scale (Lee SS) (10) is most commonly used (n=8), followed by the FACT-BMT (n=6), SF36 (n=5) and Human Activities Profile (HAP) (11) (n=4). A variety of other measures are used less frequently.

The PRO/QOL assessment is listed as a secondary objective in all but two of 29 trials. The first is a phase II GVHD prevention study in which the agent, Vorinostat is added to the standard GVHD prophylaxis of tacrolimus and methotrexate (NCT02409134) (12). As Vorinostat, an HDAC inhibitor, has been shown to have neuroprotective and neurorestorative effects in preclinical models, the authors investigated the neurocognitive function and QOL in study patients using a variety of measures in a longitudinal manner. Control subjects received either an allogeneic (without Vorinostat) or autologous transplant. The results showed that patients receiving Vorinostat had a total neurocognitive performance comparable with autologous controls, who performed better than allogeneic controls. In this study the incidence of GVHD was not reported between cases and controls. The second is the POSTAGE study, prospectively evaluating the outcomes of second-line therapies in aGVHD, which is in the recruitment phase (NCT02151539). QOL as assessed by the FACT-BMT measure is one of four primary objectives.

Of the 16 completed studies (five terminated due to slow accrual), eight (50%) have a publication of their results available, which in six (75%) cases included the PRO/QOL data (Table 3). Three unpublished trials completed within the last five months (a publication may be pending). Of the six papers which included PRO outcomes, one was for initial therapy of acute GVHD, one for initial therapy of chronic GVHD, and four for steroid-refractory GVHD.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0802 (NCT01002742) is a phase III, randomized double blind, placebo-controlled trial evaluating the addition of Mycophenolate mofetil (MMF) vs. placebo to systemic corticosteroids as initial therapy for aGVHD (13). A pre-planned futility rule was met after 235 patients were

enrolled, as MMF did not improve GVFD-free survival compared to steroids alone. The MDASI measure was completed for 103 MMF patients and 108 placebo patients, approximately 90% of patients. The total MDASI symptom severity or interference score was no different by arm.

BMT CTN 0801 (NCT01106833) is a phase II/III randomized, multicenter trial of Prednisone /Sirolimus vs Prednisone/Sirolimus/Calcineurin Inhibitor for treatment of cGVHD at first presentation. The study was launched with 3 arms, but the prednisone/sirolimus/photopheresis-arm closed prematurely due to slow accrual and the remaining 2-drug vs. 3-drug study ended in phase II for statistical futility with 138 evaluable subjects (14). QOL was measured by the FACT-BMT, SF-36 and Lee SS. Patients on the 2-drug arm had significantly better scores at 2 and 6 months as measured by the SF36 physical component summary (adjusted by baseline score) than the 3-drug arm. The FACT-BMT Physical well-being scores were also higher at 2 months on the 2-dug arm, but only in the non-adjusted analysis.

The final four studies investigated novel agents in steroid refractory GVHD. Baird et al (NCT00702689) published a pilot study investigating the impact of Imatinib in patients with sclerotic skin changes. Twenty patients were enrolled, 14 of whom were evaluable for the primary endpoint of response at 6-months, defined by changes in their range of motion (ROM). Five had a PR and seven had stable disease. ROM was not significantly associated with any functional or PRO, including grip strength, walk times, the HAP, Lee SS, SF36, and cGVHD Activity Assessment-Patient Self Report (15). Twenty-one patients were enrolled in a phase I/II study investigating response to Rituximab (NCT00136396) (16). 70% of available patients (n=20) obtained clinical responses. Nine evaluable patients had an improvement in their Lee SS score, seven of whom had also been assessed as having a clinical response. Thalidomide (NCT00075023) was tested in a phase II, randomized, placebo-controlled, double-blind trial evaluating its impact on patients with treatment-refractory oral cGVHD (17). The study terminated early, with only 10 subjects accrued. While several interesting observations were made (including some response to placebo), the small numbers precluded any firm statistical conclusions. Finally, sonidegib, a selective antagonist of the hedgehog coreceptor Smoothened, was tested in a phase I trial (NCT02086513). Accrual was terminated early due to toxicity burden (not attributed to sonidegib) and patient decisions to stop taking sonidegib. Approximately half of the patients had a clinical response (PR), and there was a significant change in the Lee SS scores between responders and non-responders – although the mean change in score within each group was not significant. The FACT-G showed no change between responders and non-responders (18). PRO completion rates are not uniformly available.

PROs in acute GVHD: progress since 2010

It is not clear that significant progress has been made in the development of a GVHD-specific PRO measure and incorporating PRO in aGVHD clinical trials, although investigators have called for the development of novel endpoints such as PROs in studies (19). Recent international consensus publications by Harris et al (20) and Schoemans et al (21) make significant strides in the standardization of terminology, diagnosis and disease

assessment in aGVHD, and while the goal was not specifically to address clinical trials or PROs, a firm foundation is laid to do so.

PROs in chronic GVHD: progress since 2010

Significant advances have, however, been made in the understanding of how to incorporate PROs into cGVHD clinical trials. Although not a clinical trial, the chronic GVHD consortium performed a prospective multicenter observational study in a cohort of HCT recipients requiring immunosuppression for cGVHD. Patients were followed every 6 months collecting both physician- and patient-reported standardized information on organ involvement and symptoms. NIH consensus scoring was reported by clinicians, and PRO were collected using the SF36, FACT-BMT, Lee SS, Human activity profile, activity scale for kids and the ocular surface disease index (22). An aim of the PRO data collection was to evaluate the measures to determine which would be most useful in evaluating GVHD symptom burden in clinical trials. Analysis of PRO at baseline (a single timepoint) showed significant differences between the PRO scores in patients with different NIH disease severity (mild, moderate, severe) and concluded that there is a significant association between PROs and NIH criteria even when adjusting for other important transplant characteristics. The SF36 and FACT-BMT performed equally well in this cross-sectional setting (23). A separate analysis addressed changes in GVHD activity over time. They found that changes in patient reported cGVHD were significantly associated with changes in PROs, that clinician-assessed cGVHD changes were associated with changes in PROs, but that changes in the NIH-assessed global cGVHD were not associated with changes in PROs. They also reported that a smaller set of questions from the FACT-BMT, the FACT-G, was as good as the full measure or the SF36 and could be used alone to reduce respondent burden; neither however correlated well with the NIH global severity scores (24).

Parallel efforts have been made to develop a PRO measure, specifically validated for use in cGVHD, which is able to assess change in the severity of cGVHD. The Lee Chronic GVHD Symptom Scale (10), developed with patient input in patients with active cGVHD, is a reliable and valid measure which been shown to be sensitive to change. The LSS is a 30-item 7-domain symptom scale, including skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy and mental and emotional, which takes a median of two minutes to complete. Studies have shown that changes in the NIH skin, eye, mouth, GI, lung and summary scales correlate with patient-reported changes in GVHD (25–29). Recently, further work has been done to re-examine the validity of the LSS in a contemporary patient cohort, towards FDA qualification of this PRO measure as a drug development tool. The results show very positive responses from participants, who reported that the scale is clear and captures almost all of their symptoms (30). Although future studies may be needed to expand the populations studied, this study strongly supports the FDA qualification of this PRO measure.

In 2015, the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. Design of Clinical Trials Working Group report (31) [martin, 2015] was published. This report focuses on considerations for the design of cGVHD treatment (not prophylaxis) clinical trials and expands and improves upon the 2006 WG

recommendations (3), by incorporating important advances in diagnosis and staging, biomarkers, histopathology, supportive care and PRO studies (such as those mentioned above) that occurred over the intervening decade. The 2015 report is focused primarily on development, characterization, validation and selection of primary and secondary endpoints for studies of GVHD treatment. Although the considerations for selecting endpoints described in the 2015 report clearly address patient-centered outcomes “.....endpoints should be selected for their ability to demonstrate clinical benefit, which can be a prolongation of survival or an improvement in the way a patient feels or functions”, there remain barriers to selecting PRO as primary endpoints, including the stringent FDA requirements mentioned above (4). Thus, while the Consensus Committee make a stronger recommendation about the inclusion of PROs than was made in 2006, it may still be considered soft, “patient-reported measures should be incorporated whenever feasible”.

Conversely, the Measuring therapeutic response in chronic graft-versus-host disease: NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report (32), makes a strong recommendation for the inclusion of a PRO, the LSS, as a ‘chronic GVHD-specific core measure’, alongside clinician-assessed and patient-reported signs and symptoms and clinician-assessed or patient-reported global rating scales. Non GVHD-specific PRO measures such as the SF36, FACT-BMT or HAP are strongly encouraged, but considered optional and should not be used as primary endpoints due to the lack of evidence of sensitivity to change for this indication (32).

An important consideration for all data in clinical trials, including PROs, is completeness and missing data. A rigorous plan, outlined in the protocol and logistically in place from study onset, to ensure timely completion of PRO with regular reminders to participants and oversight by the study team, is required. The prospectively collected PRO data in the Chronic GVHD Consortium mentioned above, had 87% completeness at baseline (23), and completeness at follow up timepoints ranging from 75-85% (33, 34). Statistical approaches to handle missing data should be included in the protocol.

Progress in the use of PROs in Clinical Trials

Guidelines for the inclusion and reporting of PROs in clinical trials

Even for clinical trials that do include a PRO endpoint, it is not uncommon to find inadequate detail in the protocol, for example on background, methodology, hypothesis and power (35) or sub-optimal reporting of the PRO outcomes in the study publication (36). A recent review (1) of almost 800 clinical trials abstracted data related to eight outcomes from recommended quality standard for reporting PRO. They found that the proportion of clinical trials who met the eight indicators ranged between 15% and 81%. This inadequate design undermines not only the ability to interpret the PRO in the context of the study, but also the confidence of the community in the value of the endpoint. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement was published in 2013 to standardize the quality of clinical trial protocols (37, 38). An extension, providing specific recommendations for items to be addressed when PROs are included as either primary or secondary endpoints, was recently published (39). This provides a number of extensions and

elaborations on the checklist provided in the initial publication. The Consolidated Standards of Reporting Trials (CONSORT) statement provides evidence-based recommendations to improve the completeness of reporting of randomized controlled trials (RCTs). The most recent CONSORT Statement, published in 2010 (40), did not specifically address PRO, however based on findings such as those mentioned above, a CONSORT-PRO extension was published in 2013 (41, 42), which describes the methodology by which the extension was developed and urges that all aspect of the PRO in the clinical trial be correctly addressed. A checklist of recommendation is provided.

Non GVHD-specific PRO measures

The HCT field has made significant efforts to harmonize the generic PRO measures which should be used in the research setting. The Design of Clinical Trials Working Group (32) recommended the SF36, FACT-BMT or HAP measures in adults. The BMT CTN has called for a core set of measurement tools for study endpoints of QOL (43), and more recently the BMT CTN and the CIBMTR prepared a consensus paper which recommended using a core set of domains from a versatile freely available single measure system, which is easy to access and has a low symptom burden. The NIH PROMIS measures were proposed as the system which met all of these requirements (44). The group went on to study the PROMIS measures in HCT survivors and compare its usefulness with that of the SF36. Results show a high degree of correlation between the SF36 and the PROMIS scores and suggest that symptoms and function can be adequately assessed using the SF36 or PROMIS measures, both in the general population of HCT survivors (45) and those with GVHD (46).

In aGVHD the MDASI has been used in some studies (2). The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) (47) is a PRO measure developed to evaluate symptomatic toxicity specifically in the context of clinical trials. The PROCTCAE is 124 items, which represent 78 symptomatic toxicities, include attributes such as frequency, severity and interference. The choice of items to include in an individual trial is determined by the expected toxicities that will be experienced and there is no need for a patient to complete the entire battery, and no summary score. The measure is freely available. The PROCTCAE may be useful for GVHD clinical trials (35), especially acute GVHD (2), which has a high burden of symptoms which are hard to the clinical team to precisely quantify (e.g. nausea and anorexia) or assess the impact of (interference due to diarrhea). There is limited experience with the PROCTCAE in HCT in general, although some data suggests it's use is feasible early post-HCT even when frequently administered (48). The PROCTCAE and PROMIS have not to my knowledge been reported in GVHD clinical trials, and there are no studies listed on clinicaltrials.gov with these search terms and GVHD.

Composite scales

Composite scales may be of great use in GVHD trials as they capture clinician assessment, PRO, as well as laboratory or functional measures. Composite endpoints have been proposed by investigators in order to fully represent that the clinical benefit obtained in a trial may encompasses not only a clearly defined primary endpoint, but also benefits in symptoms, functions and QOL associated with the primary endpoint (31). However, composite scales

are complex to develop, each component needs to be justified and show clinical benefit and sample size as well as a gold standard against which to validate the scale need to be considered. Currently no composite scales incorporating PRO in GVHD have been developed.

Conclusions

In summary, a small proportion of clinical trials in GVHD treatment and prophylaxis now include PROs, typically as secondary outcomes, but it is not always possible to find a publication for a completed trial, and publications do not always include the PRO outcomes. Additionally, PRO endpoints are often presented separately to other outcomes and may appear confusing or contradictory, and hard to reconcile clinically. Trials are frequently inadequately powered for the PRO outcome (either initially or due to accrual issues) leading to a lack of confidence in the value of the PRO results.

This is despite significant efforts by chronic GVHD investigators to incorporate PROs, and drive a patient-centered approach, in clinical trials for GVHD treatment. Reassuringly, evidence of recent adoption of the consensus recommendations may be seen in recently recruiting trials which now commonly incorporate the GVHD-specific Lee SS and the non GVHD-specific FACT-BMT and/or SF36. The Lee SS is recommended in therapeutic response trials as a chronic GVHD-specific core measure alongside other clinician and patients assessments and reports. Additionally, non GVHD-specific measures are strongly recommended as secondary outcomes. Although there is substantial experience with generic measures including the SF36 and FACT-BMT, there are some limitations to their use such as licensing requirements and higher respondent burden. Growing experience with the PROMIS measures in HCT, as well as the benefits the PROMIS system has over the currently used instruments, suggest this may become routinely used in the future.

Less progress has been made in acute GVHD with no published recommendations suggesting a standard approach to PRO collection in trials. A validated PRO measure in this setting is needed and could potentially be built using elements of the PROCTCAE. Pediatrics is also less well represented in the development of specific measures in this area. Finally, widespread support in the field for routine inclusion of PRO as primary (or even secondary) objectives in GVHD trials will require confidence in PRO results which will follow from well conducted clinical trials performed following consensus recommendations, from both GVHD and PRO experts.

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Recommendations

1. Incorporate PROs into cGVHD studies according to the recommendations set out by the NIH consensus project for criteria for clinical trials in cGVHD
2. Promote FDA qualification of the Lee Symptom Scale for cGVHD
3. Pursue the development of a validated PRO measure for acute GVHD
4. Follow the CONSORT and SPIRIT PRO extensions to ensure the protocol and publication fully describe the rationale, delivery and value of the PRO collection
5. Advance both the clinical and statistical development of composite endpoints as primary endpoints in GVHD clinical trials
6. Harmonize the measures used for non GVHD-specific PRO collection

Table 1:

GVHD prophylaxis studies listed on clinicaltrials.gov, which include Quality of Life (QOL) or Patient-Reported Outcomes (PRO) endpoints

Study	GVHD type and endpoint	Study agent/intervention	PRO primary/secondary	Measure(s)	Study status	Publication	PRO reported in publication?
NCT02409134	GVHD prophylaxis	Vorinostat	Primary (feasibility)	Cogstate PHQ-9 GAD-7 FACT-G	Completed	yes	yes
NCT00391170	Chronic GVHD prophylaxis	Topical Dexamethasone oral Solution	secondary	OHIP-14	Recruiting		
NCT03339297	Acute GVHD prophylaxis	Defibrotide	Secondary	FACT-BMT-TOI EQ-5D	Recruiting		
NCT02345850	Acute and Chronic GVHD prophylaxis	Calcineurin Inhibitor-Free Interventions	Secondary	QOL survey	Recruiting		

Computerized Cognitive Test (Cogstate); Patient Health Questionnaire (PHQ-9); General Anxiety Disorder (GAD-7); Functional Assessment of Cancer Therapy-general (FACT-G); 14-item Oral Health Impact Profile (OHIP-14); Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) – trial outcome index (TOI); QOL survey=measure not stated

GVHD treatment studies listed on clinicaltrials.gov, which include Quality of Life (QOL) or Patient-Reported Outcomes (PRO): in recruitment

Table 2:

Study	Acute/chronic GVHD	Study intervention	PRO primary/secondary	Measure(s)	Study status
NCT02151539	Acute, second-line therapy	Therapies including Extracorporeal Photopheresis	Primary (one of)	FACT-BMT	Recruiting
NCT02913261	Acute steroid refractory	Ruxolitinib	Secondary	FACT-BMT EuroQol-5D-5L	Recruiting
NCT02652130	Acute steroid refractory	Remestemcel-L (Mesenchymal Stromal cell)	Secondary	QOL survey	Recruiting
NCT03640481	Chronic	Efficacy and Safety of KD025	Secondary	Lee SS	Not yet recruiting
NCT02669251	Chronic (Bronchiolitis obliterans syndrome)	AZD9668, an Oral Neutrophil Elastase Inhibitor	Secondary	Lee SS HAP FACT-BMT 6 min walk test	Recruiting
NCT01273207	Chronic (Bronchiolitis obliterans syndrome)	Cyclosporine Inhalation Solution (CIS)	Secondary	QOL survey	Recruiting
NCT03007238	Chronic, steroid refractory	Extracorporeal Photopheresis and Low Dose Aldesleukin	Secondary	Chronic GVHD Symptom Scale	Recruiting
NCT03422627	Chronic, steroid refractory	AMG 592 (IL-2 mutein)	Secondary	SF36 Lee SS	Recruiting
NCT03112603	Chronic, steroid refractory	Ruxolitinib	Secondary	Lee SS FACT-BMT EQ-5D	Recruiting

Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT); QOL survey=measure not stated; Lee cGVHD Symptom Scale (Lee SS); Human Activities Profile (HAP); Short-form-36 (SF36)

GVHD treatment studies listed on clinicaltrials.gov, which include Quality of Life (QOL) or Patient-Reported Outcomes (PRO): completed

Table 3:

Study	Acute/chronic	Study intervention	PRO primary/secondary	Measure(s)	Study status	Publication	PRO reported in publication
NCT00929695	Acute, initial treatment	Low-Dose Glucocorticoids	Secondary	MDASI	Completed (Dec 2015)	No	
NCT02411084	Acute, steroid refractory	BEGEDINA®	Secondary	SF36	Terminated (insufficient rate of accrual)	No	
NCT01530256	Acute, steroid refractory	ALD518 (anti-interleukin 6 monoclonal antibody)	Secondary	FACT-BMT	Terminated (March 2013)	No	
NCT01002742	Acute	Steroids/Mycophenolate Mofetil vs Steroids/Placebo	Secondary	MDASI	completed	Yes	Yes
NCT02491359	Chronic	Carfilzomib	Secondary	Lee SS, HAP, SF36 FACT-BMT 2-minute walk test	Completed (Sept 2018)	No	
NCT00702689	Chronic skin	Imatinib Mesylate	Secondary	HAP SF36, Lee SS	Completed	Yes	Yes
NCT00136396	Chronic, steroid refractory	Rituximab	Secondary	QOL survey	Completed	Yes	Yes
NCT02123966	Chronic, steroid refractory	Topical Sirolimus	Secondary	OHIP-14	Terminated (slow accrual)	No	
NCT00075023	Chronic	Topical Thalidomide	Secondary	QOL survey	Terminated (unable to enroll)	Yes	Yes
NCT01287078	Chronic (Bronchiolitis obliterans syndrome)	Cyclosporine Inhalation Solution (CIS)	Secondary	QOL survey	Completed (Aug 2018)	No	
NCT02086513	Chronic, steroid refractory	LDE225 (Hedgehog signaling pathway inhibitor)	Secondary	Lee SS FACT-G	Terminated	Yes	Yes
NCT00031824	Chronic	Hydroxychloroquine	Secondary	QOL survey	Completed	Yes	No
NCT00144430	Chronic	Pentostatin	Secondary	QOL survey	Completed	Yes	No
NCT01380535	Chronic	Extracorporeal Photopheresis (ECP) Therapy	Secondary	SF36 FACT-BMT	Completed (March 2017)	No	
NCT02513498	Chronic	Isxomib Citrate	Secondary	Lee SS HAP SF36 FACT-BMT	Completed (June 2018)	No	
NCT01106833	Chronic	Sirolimus Plus	Secondary	SF36 FACT-BMT	Active, not recruiting	Yes	Yes

Study	Acute/chronic	Study intervention	PRO primary/secondary	Measure(s)	Study status	Publication	PRO reported in publication
		Prednisone and Sirolimus/ Calcineurin Inhibitor Plus Prednisone					

MD Anderson Symptom Inventory (MDASI); Short-form-36 (SF36); Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT); Lee cGVHD Symptom Scale (Lee SS); Human Activities Profile (HAP); QOL survey=measure not stated; 14-item Oral Health Impact Profile (OHIP-14); Functional Assessment of Cancer Therapy-general (FACT-G)