ABSTRACT
Positive results from recent clinical trials have significantly expanded current therapeutic options for patients with chronic graft-versus-host disease (GVHD). However, new insights into the associations between clinical characteristics of chronic GVHD, pathophysiologic mechanisms of disease, and the clinical and biological effects of novel therapeutic agents are required to allow for a more individualized approach to treatment. The current report is focused on setting research priorities and direction in the treatment of chronic GVHD. Detailed correlative scientific studies should be conducted in the context of clinical trials to evaluate associations between clinical outcomes and the biological effect of systemic therapeutics. For patients who require systemic therapy but not...
INTRODUCTION

Chronic graft-versus-host disease (GVHD) is the leading cause of late morbidity and nonrelapse mortality after allogeneic hematopoietic cell transplantation (HCT). Treatment of chronic GVHD is often ineffective, with frequent incomplete responses and recurrences [1-4]. Since the previous National Institutes of Health (NIH) Consensus Conference in 2014 [5,6], impressive advances in understanding of the biological basis of chronic GVHD have expanded treatment options [7-9]. The focus of chronic GVHD therapeutics has shifted from broad immunosuppression toward targeted therapies related to pathways relevant to the pathophysiology of the disease [10,11]. Through industry collaboration, multicenter phase 2 and phase 3 clinical trials have meanwhile investigated multiple agents for treatment of newly diagnosed glucocorticoid-refractory or treatment-refractory chronic GVHD, including ibrutinib (NCT02195869, NCT02959944, NCT03790332), ruxolitinib (NCT03112803), itacitinib (NCT03584516), belumosudil (NCT02841995, NCT03640481), and axalitimab (NCT03604682, NCT04710576).

Based on the results of a phase 2 clinical trial demonstrating an overall response rate (ORR) of 67% and a complete response rate of 21%, the US Food and Drug Administration approved ibrutinib for treatment of chronic GVHD after failure of one or more lines of systemic therapy [12-14]. This approval set the precedent for use of the 2014 NIH consensus criteria for regulatory purposes and established the pathway for future approvals.

Preliminary results of 2 large randomized studies have been presented recently. In an open-label, randomized phase 3 clinical trial, ruxolitinib demonstrated improved ORR compared with best available therapy in subjects with glucocorticoid-refractory or -dependent chronic GVHD. Ruxolitinib was associated with longer failure-free survival (FFS) and greater symptom improvement compared with best available therapy, without increased toxicity [15]. In an open-label, randomized phase 2 clinical trial for subjects with chronic GVHD previously treated with 2 to 5 lines of therapy, belumosudil resulted in high ORR (74%), and responses were both durable and clinically meaningful [16].

These studies demonstrate the feasibility of multi-institutional collaborations for chronic GVHD research and represent significant progress for the field. Nonetheless, significant challenges in the treatment of chronic GVHD remain. Glucocorticoids continue to be used for initial therapy. The addition of other agents or the continued administration of medications used for prophylaxis may have glucocorticoid-sparing effects but have not shown improved response rates in randomized studies [17-24]. Short-term and long-term clinical response rates with glucocorticoids are unsatisfactory, and prolonged administration causes significant side effects that can be as challenging as chronic GVHD itself. As such, novel approaches to initial chronic GVHD therapy warrant investigation. Furthermore, given the heterogeneity of clinical manifestations and treatment history in patients, clinical data to guide the choice of therapy are lacking. Although novel agents have expanded treatment option [25], irreversible fibrotic progression and severe immune dysfunction with serious infectious complications remain challenging [26]. Thus, many patients receive multiple lines of empirically selected treatments, with marginal efficacy and cumulative toxicities.

To advance the field, new insights are needed into how clinical manifestations or phenotypes of chronic GVHD are related to pathophysiological mechanisms that are potential targets of novel therapeutic agents [6]. Understanding the link between the clinical and biological effects of chronic GVHD therapies may enable us to overcome current barriers and allow for more biologically relevant and individualized treatment approaches.

PURPOSE OF THIS DOCUMENT

The current report is focused primarily on setting research priorities in the treatment of chronic GVHD. Owing to the relative rarity of chronic GVHD and the variety of distinct subtypes, centers and stakeholders will need to work together to enroll subjects in multicenter clinical trial protocols. This document is not meant to be prescriptive, as it is neither a review nor a treatment guideline; rather, we provide guidance regarding gaps in knowledge and suggestions for future clinical trial development for the treatment of chronic GVHD.

SUMMARY OF RECOMMENDATIONS

1. Correlative studies should address associations between clinical manifestations and biomarkers and between disease response and the biological effect of targeted therapies.
2. In clinical trials, biological samples should be collected that can be preserved for future research.
3. Broad biomarker panels should be evaluated initially in a small number of patients to inform the selection of a subsequent narrower panel of informative correlative measures.
4. When feasible, clinical trials for initial systemic therapy should investigate innovative therapeutic agents in the absence of concurrent glucocorticoid initiation.
5. Clinical trials for treatment-refractory chronic GVHD should accrue subjects early in their disease course, when clinical features, such as inflammatory or fibrotic manifestations early after onset, are more likely to be better assessed for clinical and biological response.
6. Biological prognostic biomarkers should be evaluated in clinical trials to develop a more personalized approach to treatment based on the clinical manifestations and biological profile.
7. Comparative clinical trials should be conducted to evaluate the efficacy of targeted therapies that demonstrated substantial disease activity in single-arm studies.
8. Communication and collaboration among academic medical centers, medical societies, funding agencies, and industry should be pursued to support a biology-based strategic approach.

**METHODS**

Each working group was organized to encourage global engagement in the topic [27]. Four groups worked individually beginning in February 2020 to review the relevant literature and prepare the initial draft of the manuscript. The Steering Committee reviewed and discussed the initial draft and offered recommendations for revisions. Two iterative rounds of comments and revisions were collected before the November 2020 Consensus Conference. The manuscript was further revised for submission after additional suggestions from external reviewers, consensus conference participants, and others during a 30-day public comment period.

**BIOLOGICAL CONSIDERATIONS**

Extensive preclinical small animal and human investigations have implicated certain biological pathways in the pathophysiology of chronic GVHD and helped identify therapeutic agents that may have clinical activity [11]. Significant gaps in knowledge remain, however. The association between chronic GVHD disease manifestations, such as individual organ involvement or overall disease phenotype, including inflammatory, fibrotic, and immune dysfunction features, and biological markers of pathophysiology are not well understood and should be elucidated in future studies. Furthermore, the biological impact of targeted therapeutics on the disease and the association between biological and clinical effects are not well characterized. Preliminary investigation of the biological activity of novel targeted agents has focused on the proposed mechanism of action when used for other diseases, such as hematologic malignancies or autoimmune diseases. How these agents modulate pathogenic signaling pathways in chronic GVHD is not known. Cause-and-effect testing of drug, protein/antibody, or cellular therapies can be interrogated in preclinical models chosen to best reflect clinical phenotypes and biological data.

As we better understand this clinical-biological correlation, the approach to chronic GVHD treatment could significantly change. The association of biological markers with disease manifestations could lead to algorithms that have major implications for treatment-related outcomes and clinical trial design, especially if they help refine risk stratification. Moreover, select biomarkers or panels of biomarkers could guide the selection of specific therapeutic agents and be used to monitor responses to treatment [28]. For all these reasons, future studies should expand the assessment of biological correlates in the context of clinical trial designs to close these knowledge gaps and redefine the paradigms of chronic GVHD treatment from an empirical approach to a more personalized approach (Figure 1).

**Evaluation of biological markers**

With accumulated data from multiple trials over time, it may be possible to identify more precise therapeutic targeting of particular cells, tissues, or pathways for specific organ manifestations or clinical phenotypes. Equally important, paired analysis of biomarker changes between baseline and subsequent time points after starting treatment with a selected targeted agent would be highly informative in documenting expected on-target and unexpected off-target pharmacodynamic effects [29]. The data needed for such an approach can be divided into tests that are readily available at many sites and are not cost prohibitive (Tier 1, or core studies) and others that require special equipment, sophisticated analytics, or complex sample processing or incur high cost (Tier 2, or specialized testing) (Table 1). Uniform protocols for sampling and processing of biospecimens should be used at each study site, with upfront centralized storage of samples for Tier 2 studies. Biospecimens can include peripheral blood cells, tissue biopsies of involved organs, body fluids, serum, and plasma. By collecting samples before, during, and after therapy, the feasibility and utility of an assay can be investigated in a pilot study, leading to the identification of a more focused panel of tests for follow-up studies. Efforts to validate previously identified biomarkers are important and could be done as Tier 1 or Tier 2 tests, depending on the nature of the test. Tier 2 studies may be best suited for discovery-based analysis [29].

**Sample collection and analysis**

Serial samples should be collected at the time of chronic GVHD diagnosis before starting any systemic therapy, at a time that would be informative in assessing immediate drug effects depending on the agents investigated, and then later to correlate with clinical response. Expert clinical assessment and data acquisition are needed. Material storage in a biorepository facilitating a communal effort to perform individual assays in a standardized fashion would enable quality control assessment, avoid the need for real-time assays, reduce costs, minimize sample-to-sample variation, and ensure the availability of expertise for implementation and interpretation of an analysis. A strong research infrastructure at each site is needed for the acquisition, processing, and storage of biological samples, together with a governance process to distribute centrally

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**Table 1**

| Incorporation of Biological Markers into Clinical Trials in Chronic GVHD |

<table>
<thead>
<tr>
<th>Examples of tier 1 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometry of peripheral blood cells to evaluate the maturation, differentiation, and function of T cells, NK and NKT cells, B cells, plasma blasts and plasma cells, dendritic cells, monocytes, and macrophages</td>
</tr>
<tr>
<td>Histopathologic and immunohistochemical testing to evaluate biopsy specimens of involved tissue</td>
</tr>
<tr>
<td>Bioasays and immunooassays to evaluate cytokines, chemokines, and autoimmune antibodies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of tier 2 studies</th>
</tr>
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<tbody>
<tr>
<td>Mass cytometry to evaluate intracellular signaling and transcription factor expression</td>
</tr>
<tr>
<td>Single cell RNA-seq, CITE-seq (allows assessment of cell surface proteins), and ATAC-seq (allows assessment of chromatin accessibility)</td>
</tr>
<tr>
<td>Mass spectrometry to identify proteins or metabolites</td>
</tr>
<tr>
<td>Multiplexed immunofluorescence (eg, CODEX) to define spatial relationships between subsets of infiltrating donor-derived cells, recipient cells of various types, and the extracellular matrix</td>
</tr>
<tr>
<td>Spatial transcriptomics (eg, seqFISH) to characterize gene expression profiles without disruption of spatial tissue context</td>
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<tr>
<td>Intestinal microbiomics</td>
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</tbody>
</table>

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**Figure 1.** Pathophysiologic pathways interface between clinical manifestations and biological profiles of patients with chronic GVHD at time point 0 (T0, prior to treatment start or change) and time point 1 (T1, following treatment). The goal of the proposed chronic GVHD clinical study design is to determine the association between these 3 essential elements—clinical manifestations, biomarker profile, pathophysiologic inferences—and how they change from T0 to T1.
stored samples and clinical data. As data are collected, the number of tests could be narrowed down to those that are most informative for understanding GVHD pathogenesis and the effects of specific therapeutic interventions.

**INITIAL THERAPY**

The goals of treatment for chronic GVHD are numerous: to reduce symptom burden, control objective manifestations and prevent progression of disease activity, preserve function by preventing irreversible damage and the resulting impairment and disability, and, ideally, to improve quality of life and survival and accelerate the development of immune tolerance that would allow withdrawal of all systemic immunosuppressive treatment without recurrent disease. In addition, these benefits must be sustained until systemic treatment is no longer needed, and treatment must provide a high therapeutic index in which benefits outweigh side effects.

Up to now, nearly all clinical trials of initial treatment for chronic GVHD have tested a study drug given in conjunction with glucocorticoids. None of the previous randomized trials has shown improved response rates by adding another agent to glucocorticoids for initial treatment of chronic GVHD [20,21,30,31]. Nevertheless, the biological effects of systemic glucocorticoids in chronic GVHD are not well understood, and their concurrent use blunts the ability to assess the objective pathophysiologic impact of other study interventions on signaling pathways and other potential mechanisms. Thus, initiation of systemic monotherapy of chronic GVHD without glucocorticoids is the optimal setting in which to investigate the clinical and biological impacts of an individual therapeutic agent. Furthermore, successful minimization or elimination of glucocorticoid use for initial treatment of chronic GVHD would constitute a major accomplishment for glucocorticoid use could be explored in upfront treatment trials, such as the use of lower glucocorticoid starting doses (0.25 mg/kg/day) in all subjects or a shorter duration of exposure (taper off glucocorticoid within 1 to 3 months after initiation), multiple clinical considerations support the proposed glucocorticoid-free novel approach. First, chronic GVHD has an insidious onset in most patients and typically does not necessitate urgent intervention. Second, glucocorticoids are effective in only approximately one-half of patients, and treatment causes considerable toxicity, so omission of concurrent glucocorticoid administration could be beneficial even if the response to monotherapy were delayed. Third, concurrent glucocorticoid treatment masks the treatment effect of the interventional agent, because clinical manifestations improve initially in most patients after starting glucocorticoid treatment, but the proportion of patients with FFS and durable responses at 1 year has been estimated at <20% [32]. The availability of new targeted agents with more broadly immunomodulating and anti-inflammatory effects further supports this approach.

**Eligibility Criteria**

Inclusion criteria should articulate the characteristics of patients deemed to require systemic treatment and be tailored to the research question. Moderate to severe chronic GVHD by the NIH criteria is a clear indication for systemic treatment [33]. In addition, mild chronic GVHD by the NIH criteria can be an indication for systemic treatment if prespecified high-risk features such as progressive onset or low platelet count are present [33,34]. Furthermore, the availability of less toxic systemic therapies may justify the treatment of mild chronic GVHD to prevent progression to more severe forms of the disease. Enrollment of patients with a broad spectrum of chronic GVHD manifestations and all clinical phenotypes will facilitate efforts to identify relationships between specific organ manifestations, clinical phenotypes and laboratory correlates. We recommend that administration of medications used to prevent or treat acute GVHD should be continued for monotherapy trials, but eligibility criteria should specify a time period during which treatment regimens should remain stable before beginning any study intervention. Finally, special considerations should be made for children, since the characteristics of immune reconstitution and chronic GVHD evolution in children differ from those in adults [35].

**Clinical Endpoints**

The primary endpoints in phase 1 studies of initial monotherapy for chronic GVHD should be safety and feasibility. A clinical trial design that investigates multiple dose levels, coupled with pharmacokinetics and pharmacodynamics if not already known, will help identify the ideal dose for subsequent trials, based on pharmacokinetics, pharmacodynamics, therapeutic effect, and safety profile. Safety considerations include well-defined stopping rules for both futility and unacceptable toxicity. The primary feasibility endpoint should assess the proportion of subjects who remain glucocorticoid therapy-free at a specified time point, such as 4 to 8 weeks after initiation of treatment. Participants must be given glucocorticoids or other approved or established effective treatment if clinical evaluations indicate disease progression or insufficient improvement as assessed by the investigator or reported by the patient, even if clinical changes do not meet the definition of progression by the NIH response criteria [36]. For example, glucocorticoids or other effective treatment must be started if no improvement (stable disease or mixed response) is observed within a prespecified time after starting treatment with the investigational agent or if no complete or partial response is obtained within 6 months after study enrollment. Information about glucocorticoid treatment must be documented, including the start date, clinical indications, dosing, and duration. This information will enable subsequent analyses to evaluate the cumulative glucocorticoid exposure during the first 3 to 6 months of chronic GVHD therapy, unlike in currently standard clinical practice.

For phase 2 studies with an established safety profile, primary efficacy endpoints should incorporate organ-specific and overall NIH consensus response criteria [36] at reasonable time points, such as 3 months after enrollment, and any unplanned steroid treatment should be documented. Biological correlates also can be included in the primary endpoint.
Secondary clinical endpoints can incorporate FFS [2], including details of response such as time to response, durability, organ-specific responses, patient-reported outcomes (PROs), relapse, nonrelapse mortality, survival, and correlation of clinical response with biological endpoints (Table 2). Assessment of organ-specific responses are sometimes more challenging in pediatric populations. Time to expected response, based on chronic GVHD phenotype, is an important consideration. Cutaneous erythema, oral manifestations, transaminase elevation, and diarrhea would be expected to improve within weeks after starting effective treatment, whereas measurable improvement of cutaneous sclerosis, fasciitis, and joint disease would take much longer, and manifestations of damage, such as oral and ocular sicca, bronchiolitis obliterans syndrome, and vitiligo, might not improve even though progression could be halted by effective treatment. Previous studies have shown that the median interval from the onset of systemic treatment to permanent withdrawal of all systemic treatment in patients with chronic GVHD exceeds 2 years [2,3]. Initial responses by NIH criteria limited to assessments at 3 or 6 months after starting treatment might not be durable. For this reason, phase 2 studies should follow participants for long-term outcomes (ie, at least 1 year) to ensure that responses are sustained over this period [32].

**Safety Considerations**

Initial therapy of chronic GVHD without concurrent glucocorticoid treatment differs from the long-established empirical standard of care. For this reason, providers may hesitate to offer monotherapy trials with targeted therapeutics because of concerns about withholding effective treatment. However, subjects enrolled on these trials may receive glucocorticoids at the discretion of the treating clinician whenever deemed clinically necessary and when prespecified by the protocol. The criteria for introduction of glucocorticoids must be well defined in each trial, including timing, dose, tapering schedule and duration. The committee recommends that only centers with excellent study infrastructure allowing continuous patient care, experience with clinical phase 1 studies, and the ability to perform Tier 1 and Tier 2 studies should embark on glucocorticoid-free initial therapy protocols. For optimal protection of participant safety, glucocorticoid-free protocols should require prompt reporting of glucocorticoid treatment to study personnel (eg, principal investigators, data safety monitoring board) so that well-defined stopping rules for futility can be implemented in a timely manner according to prespecified criteria. A hypothetical single-arm phase 2 efficacy study design of glucocorticoid-free monotherapy with an efficacy measure that reflects benchmarked potential clinical benefit is included as online Supplementary Material.

### BEYOND INITIAL THERAPY

Even as glucocorticoid-free trials for initial treatment advance the field, studies of glucocorticoid-refractory and treatment-refractory chronic GVHD will be needed. Well-designed studies could broaden our understanding of interactions among clinical phenotype, therapeutic response, and mechanism of action of a given agent in treatment-refractory

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**Table 2**

Clinical Trial Consideration for Initial Therapy and Beyond Initial Therapy of Chronic GVHD

<table>
<thead>
<tr>
<th>Eligibility considerations</th>
<th>Initial Therapy (Glucocorticoid-Sparing)</th>
<th>Beyond Initial Therapy</th>
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<tbody>
<tr>
<td>Broad eligibility to assess response across all clinical phenotypes and organ manifestations</td>
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<td>Avoid advanced chronic GVHD with irreversible manifestations that may underestimate benefits of investigational agent</td>
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<tr>
<td>If acute GVHD present, must be well-controlled with stable therapy for at least 2 weeks</td>
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<td>Consider eligibility criteria that allow studies to focus on more homogenous populations</td>
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<tr>
<td>Endpoints</td>
<td></td>
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<tr>
<td>Safety and feasibility</td>
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<tr>
<td>Efficacy</td>
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<tr>
<td>○ Clinical response (NIH consensus criteria)</td>
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<td>Maximize the chance of a measurable response by excluding subjects with irreversible manifestations</td>
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<tr>
<td>○ Duration of response</td>
<td></td>
<td>Allow for focused evaluations of response in more homogenous cohorts of subjects (similar clinical manifestations or treatment history)</td>
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<tr>
<td>○ Corticosteroid utilization</td>
<td></td>
<td>Correlate clinical response in defined manifestations with biological endpoints</td>
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<tr>
<td>○ Survival endpoints</td>
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<td>○ Failure-free survival</td>
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<tr>
<td>○ Nonrelapse mortality</td>
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<tr>
<td>○ Patient-reported outcomes</td>
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<tr>
<td>○ Exploratory biological endpoints</td>
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<tr>
<td>Strengths</td>
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<tr>
<td>Absence of upfront glucocorticoids maximized potential to evaluate biological impact of therapy and its clinical correlation</td>
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<tr>
<td>Challenges the current standard treatment paradigm</td>
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<tr>
<td>Subsequent clinical trial considerations</td>
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<tr>
<td>Comparative clinical trials should be conducted for agents that demonstrate disease activity in single arm studies.</td>
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<tr>
<td>Develop clinical trials that incorporate biological markers into eligibility criteria and study endpoints to evaluate individualized approaches to treatment.</td>
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Glucocorticoid Considerations

Refining eligibility criteria in studies of refractory chronic GVHD can help identify more homogeneous populations in which the clinical and biological impact of therapy can be better assessed. First, a key factor to consider is the dose and duration of prior glucocorticoid therapy, because it can be much more difficult to detect a clinical response in patients who have been heavily treated for longer periods. Definitions of glucocorticoid-refractory, -intolerant, and -dependent diseases are currently used in studies that define the minimum criteria for glucocorticoid exposure and response without providing an upper limit [33,36,37]. Studying patients early after disease is determined to be glucocorticoid-refractory is recommended to increase the likelihood of observing a clinical response or detecting a biological effect. Second, the distinction between glucocorticoid-refractory (progression during treatment with prednisone at ≥1 mg/kg/day for 1 to 2 weeks or stable GVHD on ≥0.5 mg/kg/day of prednisone for 1 to 2 months) [37] and treatment-refractory (progression of GVHD under treatment, based on an objective increase in stage/grade or new organ involvement or on a lack of improvement in GVHD compared with baseline or loss of response, defined as objective worsening of GVHD as determined by increase in stage/grade or new organ involvement at any time after initial improvement) [38], should be clearly defined. These 2 groups may differ biologically and clinically, leading to the possibility of erroneous dismissal of an otherwise effective agent. The 2014 Clinical Trial Working Group Report suggested criteria for defining glucocorticoid-refractory chronic GVHD [5], and recent efforts have been made to provide new definitions for treatment-refractory acute GVHD following the Food and Drug Administration approval of ruxolitinib [38,39].

Finally, how best to handle immunosuppressive therapies at the time of enrollment into a clinical trial after treatment failure remains an open question. As new therapies with a higher potential for efficacy and a glucocorticoid-sparing effect enter the treatment landscape, it becomes increasingly important to address this issue in the study design. Should immunosuppression be tapered, discontinued, or maintained at the beginning of therapy? Should short courses of pulsed glucocorticoids be allowed for a predefined period? Could specific dosing regimens lead to a reduction in the cumulative dose administered over time? These key considerations should be addressed and specified in clinical trial designs. Given the heterogeneity in glucocorticoid management practices in salvage trials of treatment-refractory chronic GVHD, minimization of glucocorticoids should not be considered a major study endpoint.

Chronic GVHD Phenotype and Duration

The manifestations of chronic GVHD change over time, usually becoming more difficult to reverse due to progressive organ involvement and the fibroproliferative nature of more advanced stages of the disease. Given the often refractory nature of chronic GVHD beyond front-line therapy, this setting opens opportunities to explore combinations of novel targeted agents with nonoverlapping toxicities and mechanisms of action to improve efficacy and safety. To maximize the chance of observing meaningful measurable responses to therapy (eg, as documented by PROs), we recommend prioritizing clinical trials that enroll patients with earlier disease stages. Disease-related characteristics such as inflammatory or fibrotic phenotypes are important to consider in defining eligibility. These could be used to select cohorts of subjects with a common clinical phenotype in which a specific pathophysiologic pathway of disease or treatment effect could be observed. Another option would be to include all patients with multiple concurrent features of chronic GVHD and to correlate biological data and clinical responses according to specific phenotype categories. This would allow enrollment of most patients with treatment-refractory chronic GVHD and thereby move the field toward a more personalized approach based on clinical presentation and biological profile.

Clinical Endpoints

The definition of clinically meaningful endpoints in glucocorticoid-refractory or treatment-refractory chronic GVHD studies remains challenging and should incorporate not only clinical response assessments, but also PROs. Other factors that guide the choice of clinical endpoints are the type of intervention, study phase, indication (ie, glucocorticoid- or treatment-refractory) and safety considerations. The efficacy of any new chronic GVHD therapy beyond glucocorticoids has two main components: response and glucocorticoid-sparing effect. ORR (based on NIH consensus response criteria [36]) after 3 or 6 months of therapy has been used in recent trials [40]. Since most responses in this setting are partial responses that can vary widely, additional measurements, including organ-specific responses, PROs, and biological correlates, should be assessed. Arrested progression of fibrotic manifestations could be an endpoint in studies with patients who have a well-documented history of inexorable worsening before trial enrollment. Time to response and durability of response beyond 6 months and their implications for additional therapies, glucocorticoid-sparing effect and 1-year survival outcomes provide additional indications of clinical benefit, so these assessments should be incorporated whenever possible (Table 2). Measurement of a glucocorticoid-sparing effect in advanced chronic GVHD is almost as relevant as response in defining efficacy, although glucocorticoid dose reduction per se does not qualify as evidence of clinical benefit from a regulatory perspective and is difficult to interpret in the absence of a double-blinded trial design. Although standard metrics for measuring a glucocorticoid-sparing effect have not been developed, the magnitude, incidence, timing, and durability of glucocorticoid dose reduction should be documented. The cumulative incidence of discontinued glucocorticoid treatment and its durability also should be reported.

Important secondary endpoints, such as infection, readmission rate, and measures of function and disability, are particularly relevant to more advanced chronic GVHD and should be reported whenever possible. Because most of these studies are of single-arm design, standardization of clinical endpoints is critical. Master protocols as templates with accepted inclusion and exclusion criteria, endpoints, and timelines for biosampling and response assessment could be established by the chronic GVHD research community, thereby allowing comparison of results with different targeted therapeutics. Additional endpoints specific to a given targeted therapy could be added to such protocols as needed. Communication and collaboration among academic medical centers, medical societies, funding
agencies and industry is necessary to achieve consistency and comparability across clinical trials.

**Safety Considerations**

Evaluation of the safety and tolerability of novel agents in more heavily pretreated and fragile populations remains an important goal of future studies. Because chronic GVHD is associated with high disease burden and morbidity for extended periods, the potential benefit of targeted therapy, including glucocorticoid-sparing potential, must outweigh the side effects and burden of current treatment. In trials that predominantly enroll heavily pretreated patients or patients with more advanced chronic GVHD, safety stopping rules should be designed to incorporate relevant treatment-emergent adverse events and other outcomes such as recurrent malignancy or survival.

**SUBSEQUENT CLINICAL TRIAL DEVELOPMENT**

In the short term, therapeutic agents with clinical efficacy in chronic GVHD will continue to emerge from ongoing and future clinical trials. Most of these studies will have been conducted as phase 1 or 2 trials in heterogeneous patient populations without a comparison arm. In view of the rarity of the disease, well-designed phase 2 trials that show unequivocal safety and efficacy could be considered pivotal for regulatory approval. The Working Group recommends adaptive trial designs that can improve study efficacy by increasing the number of participants allocated to maximally effective treatment arms and shortening the length of trials by quickly eliminating ineffective interventions [41,42]. Adaptive designs may be most appropriate for go/no-go decision making or efficacy testing trials, particularly in early drug development. Multiple targeted therapeutics could be investigated in parallel in small- to medium-sized phase 1 studies of glucocorticoid-free initial therapy or treatment-refractory chronic GVHD together with pharmacokinetics, pharmacodynamics, and other biomarkers to gain insight into the mechanism of action of a selected agent and its effect on the pathophysiology of the disease in a short period. Master protocols can improve efficacy by allowing participants to potentially qualify for several arms rather than screening large numbers of patients to identify a rare population of interest [43]. The aim of these trials would be to assess the association of the clinical phenotype and underlying pathophysiology with the novel agents’ biological and clinical effects. Future trials could then consolidate data for the various phenotypes, investigate biomarkers more selectively or be continued as an extension trial.

The more promising agents could then be investigated in the context of randomized clinical trials whenever necessary. For example, in upfront systemic treatment, 2 separate large phase 3 randomized clinical trials are investigating ibritinib (NCT02959944) and itacitinib (NCT03584516) compared with placebo, each in combination with glucocorticoids for moderate to severe chronic GVHD. If a novel agent demonstrates safety and encouraging clinical efficacy in a glucocorticoid-free study design as described above, then a follow-up study could compare the successful treatment modality with more established therapeutic options. For patients with treatment-refractory chronic GVHD, a trial could randomize participants to treatment with the investigational agent versus best available therapy, as has been done in the investigation of ruxolitinib for the treatment of glucocorticoid-refractory acute GVHD (NCT02913261) [44] and chronic GVHD (NCT03112603) [15]. Another approach would be to use common control groups across multiple studies as a comparator for each targeted agent to decrease the number of participants assigned to control treatments and thereby increase the proportion receiving investigational agents [45].

All trials should continue to include correlative laboratory measures to evaluate differences in baseline biomarker profiles and longitudinal changes after treatment. In the long term, multiple clinical trials with extensive correlative studies will begin to elucidate the relationships between biological and clinical responses.

**CONCLUSIONS**

Treatment options for patients with chronic GVHD have expanded considerably in recent years, led by unprecedented large multicenter randomized trials through collaboration with industry. However, despite these advances, our understanding of interactions between clinical chronic GVHD manifestations and targeted therapies directed at the pathophysiologic pathways that have been identified in preclinical models or correlative laboratory studies remains rudimentary. Efforts should continue to prioritize the assessment of biological correlates in the context of clinical trial designs that will maximize the ability to close these knowledge gaps and eventually redefine treatment paradigms of chronic GVHD into a more personalized approach. Within the next 3 years, clinical trials should challenge the current standard of care for initial systemic therapy by investigating targeted therapeutics in glucocorticoid-free study designs. Novel agents demonstrating meaningful clinical response should then be tested along with other extensively evaluated therapeutic agents. Effective partnerships among academic medical centers, industry, patient advocates, and nonprofits, including the guidance of regulatory agencies, will be necessary to speed progress in developing new chronic GVHD therapies.

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SUPPLEMENTARY MATERIALS

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APPENDIX: 2020 NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD STEERING COMMITTEE

Chairs: Steven Pavletic, MD, MS, National Cancer Institute; Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center and the University of Washington; Kirk Schultz, MD, University of British Columbia; and Daniel Wolff, MD, University of Regensburg

Members: Hildegard Greinix, MD, University of Graz; Sophie Paceseny, MD, University of South Carolina; Bruce Blazar, MD., University of Minnesota; Stefanie Sarantopoulos, MD, PhD, Duke University; Joseph Pidala, MD, PhD, Moffitt Cancer Center; Corey Cutler, MD, MPH, MPH, Moffitt Cancer Center; Gerard Socie, MD, PhD, St-Louis Hospital, Paris; Paul J. Martin, MD, Fred Hutchinson Cancer Research Center and the University of Washington; and Meredith Cowden, MA, LPCC-S, Cowden Foundation.

Treatment of Chronic GVHD Working Group 3

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REFERENCES


