



2020 NIH Chronic GvHD Consensus Project on Criteria for Clinical Trials IV - The 2020 Highly morbid forms report

November 18–20, 2020, Daniel Wolff & Sophie Paczesny



Financial Disclosure

DW received honoraria from Novartis, Neovii, Gilead, Maco, and
Mallinckrodt

SP has a patent application on “Methods of detection of graft-versus-host disease” licensed to Viracor-IBT laboratories, and a patent (10571478) on
“Biomarkers and assay to detect chronic graft versus host disease”



NATIONAL CANCER INSTITUTE

Contributors

S.J. Lee, S.Z. Pavletic, K. Schultz

Skin: Vedran Radojcic, Resat Cinar, Robert Lafyatis, Rachel Rosenstein, Edward W. Cowen

Lung: Guang-Shing Cheng, Ajay Sheshadri, Kirsten Williams, Anne Bergeron, Sarah Anand,
Jamie Todd

Ocular: Sandeep Jain, Philipp Steven, Yoko Ogawa, Daniel Saban, Luo Zhonghui

GI: Takanori Teshima, Geoffrey D. E. Cuvelier, Ernst Holler, Shannon R McCurdy, Robert Jenq

CNS: Bianca Santomasso, Kelli MacDonald, Robert Zeiser, W. Taylor Kimberly

Peripheral Neuropathy: Ervina Bilic, Klemens Angstwurm, Iago Pinal-Fernandez

Endothelial System: Olaf Penack, Michelle Schoettler, Nelson Chao, Thomas Luft

Pediatric: David Jacobsohn, Patient Advocacy: Meredith Cowden

Trial design: Linda M. Griffith



Introduction

- Definition: highly morbid forms selected are frequent and either non-reversible & impair quality of life or are associated with increased mortality
- Some morbid organ manifestations may be already non-reversible early in the course (ocular) or may serve as prognostic “gatekeeper” for the subsequent course (GI)
- Despite the known heterogeneity, cGVHD is currently treated in a homogenous fashion independent of time point, biology (inflammatory conditions vs. fibrotic conditions) and organ pattern (skin vs eye vs lung)



Purpose of the document

Outline research goals for frequent highly morbid forms of cGVHD

- advanced skin sclerosis/fasciitis (morbidity)
- Lung (morbidity & mortality)
- gastrointestinal (GI) involvement (mortality)
- Ocular (morbidity)

Research goals for other morbid conditions will be proposed in a separate taskforce manuscript

- Neurocognitive impairment and CNS-manifestations
- Peripheral neuropathy
- Endothelial damage
- Other associated manifestations

Advanced skin sclerosis / fasciitis / muscle cramps - epidemiology

- Skin sclerosis affects 20% of patients surviving 3 years and is the most frequent manifestation of severe cGVHD (Inamoto 2013) leading to functional impairment and skin breakdown
- Skin sclerosis rarely presents upfront but as the result of long-lasting inflammation
- Skin sclerosis manifests with heterogeneous pattern (primary skin isolated fascial involvement)
- Frequently accompanied by immunological and compression damage peripheral nerves incl. painful muscle cramps
- Skin sclerosis is rarely completely reversible





Advanced skin sclerosis / fasciitis / – current gaps of knowledge



- Classic endpoints (PR/CR) are not appropriate for clinical trials in sclerosis and tools to objectively quantify sclerosis are lacking (currently only P-ROM and NIH 10point scale available) (Curtis 2020)
- Role of alloreactive T cells in established sclerosis (role of effector T cells vs. Tregs)? (Berrie 2012 & Koreth 2011)
- Contribution of humoral host reactive immunity in initiation and established sclerosis (PDGF-R Antibodies, inflammatory damage)? (Svegliati 2007 & Chen 2011)
- Role of myeloid cells (macrophages, myeofibroblasts) in the process of sclerosis incl. role of TGF-beta and Interferon type I signals? (Alexander 2014, Banovic 2005, MacDonald 2017)
- Role of hedgehog, Wnt, and endocannabinoid morphogen signaling system in sclerosis? (Diestler 2019, Zerr 2012, Radojcic 2019, Cinar 2020)



Advanced skin sclerosis / fasciitis / – Roadmap



- Develop novel tools for better measurement and documentation of change in skin sclerosis for clinical trials. Refinements of the current 2014 clinical response criteria are needed for skin sclerosis/fascia manifestations
- Test emerging therapies being developed for organ fibrosis and supported by biological insights in ScGVHD, focusing on early intervention (see table slide 10)
- Test combination therapies targeting multiple pathways active in fibrosis to augment efficacy while minimizing toxicities



Advanced skin sclerosis / fasciitis / – Roadmap



- Perform longitudinal multicenter studies to test pathologic cell populations in lesional skin and peripheral blood incl. cytokine and chemokine responses
- Apply NGS strategies, including single-cell RNA-, ATAC-, TCR-, and BCR-seq to query skin biopsies to provide biological insight into the mediators of ScGVHD
- Analyze differences in mediators and targets (epidermal, dermal, fascia, nerves)
- Address disease heterogeneity - phenotype & origin of expanded T cell and B cell populations as well as extracellular matrix for molecular heterogeneity (transcriptional and epigenetic) to identify biomarkers and therapeutic targets

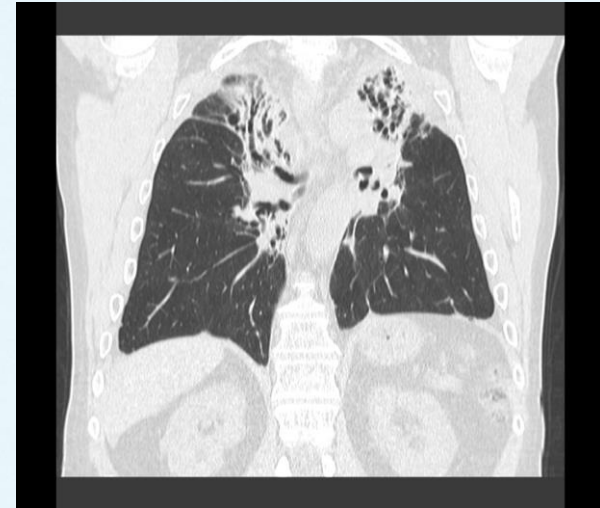
Current clinical trials targeting morbid forms



Target	Drug(s)	Target cellular subsets	Clinical Development Status
CTGF/CTN2	Pamrevlumab	Fibroblasts	Ph-3- IPF
Autotaxin	Ziritaxestat	Fibroblasts	Ph-3- IPF
HSP47	ND-L02-s0201	Fibroblasts	Ph-2- IPF
Pentraxin 2 (agonist)	PRM-151	Fibroblasts, Macrophages	Ph-2- IPF, Ph-2- Myelofibrosis
CB₂R	Lenabasum, (Ajulemic ac.)	Fibroblasts, T cells, Macrophages	Ph-3- Systemic Sclerosis
CB₂R /PPARγ	EHP-101	Fibroblasts, Endo. cells, Macroph.	Ph-2- Systemic Sclerosis
CB₁R /iNOS	MRI-1867	Fibroblasts, T cells, Macrophages	Ph-1
Oncostatin M (antagonist)	GSK2330811	Fibroblasts, Endothelial cells, T cells, Macrophages	Ph-2- Systemic Sclerosis
TGFβ	AVID200	Fibroblasts, T cells, Macrophages	Ph-1- Myelofibrosis, Ph-1- Systemic Sclerosis
IL-6R	Tocilizumab	Fibroblasts, T cells, Macrophages	Ph-3- Systemic Sclerosis, Ph-2- Steroid dependent immune disorders
CSF-1R	Axatilimab, (SNDX-6352)	Macrophages	Ph-2- cGVHD
ROCK2	Belumosudil, (KD025)	T cells, Macrophages	Ph-2- cGVHD, Ph-2- Systemic Sclerosis
Interferon receptor type 1	Anifrolumab	T cells, Macrophages	Ph-3- Systemic Lupus Erythematosus Ph-2- Rheumatoid Arthritis

Lung GVHD- epidemiology

- Affects ~ 3-10% of HCT survivors (14% of patients with cGVHD) (Bergeron 2018)
- BOS is currently the only NIH defined form of lung GVHD although restrictive changes are observed (Jagasia 2015)
- Early onset results in worse prognosis (Bergeron 2018)
- 50% mortality at 5 years (Cheng 2016 & Bergeron 2018)
- Associated with dismal QoL and physical functioning
- Asymptomatic until it gets moderate (children asymptomatic until severe) – requires screening of asymptomatic patients





Lung GVHD – current gaps of knowledge



- Sensitive tools for early diagnosis (children!) and response assessment are lacking
- Definition of biological phenotypes of BOS (is lymphocytic bronchiolitis early stage or different entity, does biology or/and time of intervention drive prognosis?)
- Definition of restrictive phenotypes of lung changes and relation to cGVHD (parenchymal vs. extrapulmonary restriction, toxicity vs. GVHD)
- Except FAM and bronchodilators no lung specific treatment has been explored while biomarkers indicate a potential distinct biology compared to other forms of cGVHD
- Identification of drivers and targets of BOS (CD4+ T cells, B cells, macrophages)?
- Interaction of microbiome and BOS?

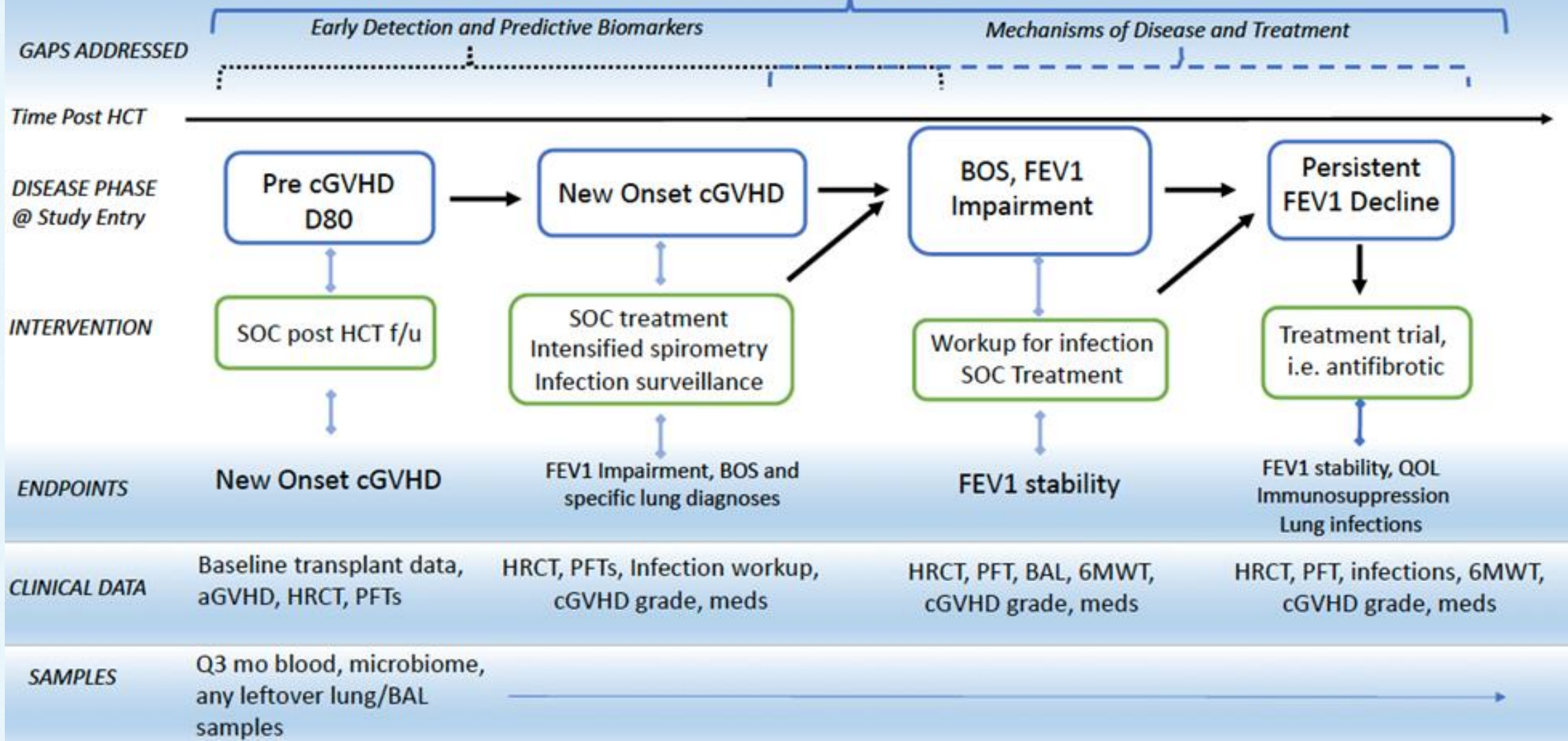


Lung GVHD – Roadmap

- Document longitudinal multicenter patient cohorts starting at cGVHD onset for clinical phenotyping, classification and epidemiology of lung GVHD subtypes (disease history, PFT, infections, chest CT, and lung histology, quantitative lung imaging techniques)
- Develop clinically relevant endpoints: FEV1 stability (or lack of progression of FEV1 decline), infectious exacerbations, exercise tolerance, quality of life, reduction of systemic steroid use, and overall survival) See suggestion of a trial in next slide
- Create a shared lung-specific biorepository for biomarker discovery and mechanistic studies (bronchoalveolar lavage, plasma/serum and lung biopsy specimens)
- Explore targeted anti-inflammatory agents and antifibrotics before severe BOS forms develop incl. knowledge of natural progression, pathogenesis and biomarkers of response

Lung GVHD – time & stage dependent sequential trial proposal

Natural History and Phenotypes




GI GVHD- epidemiology

- Incidence of esophageal (16%), upper GI (20%), and lower GI (13%) (Pidala 2013)
- GI-involvement (overlap) is associated with increased mortality although patients rarely die directly from GI-manifestations (Inamoto 2014)
- Children appear to be especially vulnerable for unknown reasons (Cuvelier 2019)
- Additional impaired exocrine pancreas insufficiency is observed
- Elevated Reg3 alpha (Shannon 2020) and decreased microbiome diversity is associated with subsequent cGVHD indicating a potential role of microbiome (Markey 2020)



Takashi 2018



GI GVHD – current gaps of knowledge

- How do early GI manifestations drive subsequent mortality?
- Why are fibrotic changes of the upper and lower GI tract relatively rare but frequent in the esophagus?
- What is the role of the microbiome in initiation of late aGVHD vs overlap vs classic cGVHD and the subsequent course of the disease
- Register trials may still suffer from misclassification of overlap vs. late acute GVHD while biomarker analyses indicate distinct biology



GI GVHD – Roadmap



- Enforcement of the NIH 2014 terminology (acute versus chronic GVHD with overlap subtype of cGVHD) across studies. The severity of individual GI manifestations should be recorded applying the response criteria not only at the time of diagnostic onset, but over time and in response to therapeutic strategies.
- Collect blood and stool samples in either natural history cohorts or interventional clinical trials to allow study of human GI-cGVHD which includes metabolome and microbiome analyses including sufficient sampling and follow up of aGVHD trials
- Generate experimental models able to address the role of dysbiosis, intestinal inflammation and subsequent cGVHD including other organ manifestations.

Ocular GVHD - epidemiology

- Incidence of ocular cGVHD is ~ 30% (Grube 2016) with 10% of cGVHD patients developing severe forms
- Ocular GVHD may affect different parts of the eye (Meibomian-, lacrimal glands, goblet cells and cornea and conjunctival surface) explaining in part different courses and symptoms
- Ocular GVHD is frequently non-reversible from the beginning but during the early course difficult to distinguish from pre-existing dry eye disease or toxicity
- Ocular sensitivity may be impaired in GVHD (Wang 2010)

(Gerber-Hollbach, N. 2020)



Ocular GVHD is not dry-eye disease



		Dry-eye disease (DED)	Ocular GVHD (oGVHD)
Cause	Known immunological mechanisms	Autoimmune Th17, CD4+/CD8+ T-cell activation through extrinsic or intrinsic triggers, unknown antigen	Migration and activation of donor hematopoietic /mesenchymal stem cells
	Fibrosis	Not typical for dry-eye disease	Early activation of fibroblasts and macrophages
Time course		Slow progress in a majority of cases	progresses within weeks to month
Impact on visual function		Mild to severe impact, blinding disease very rare	Mostly severe, if untreated, often blinding disease
Clinical findings	Filamentary keratitis	Rare finding, only in severe cases, mostly Sjögren Syndrome	Common finding, presumably caused by innate immune syst.
	Fibrosis	Rare finding	Frequent finding
	Correlation between signs and symptoms	Low correlation: strong symptoms, weak clinical signs	Low correlation: weak symptoms, strong clinical signs



Ocular GVHD – current gaps of knowledge

- Lack of diagnostic / prognostic biomarker in the absence of diagnostic signs
- Endpoints of clinical trials used in Dry Eye Disease fail in oGVHD
- Reason for heterogeneous courses unclear (some stay mild, others progress to severe)?
- Role of initiating factors (pre-existing condition, toxicity, infections)?
- Optimal intervention strategy (step up vs. step down)?
- Interaction of innate immunity and adaptive immunity – role of myeloid cells & fibroblasts in fibrosis?



Ocular GVHD – Roadmap



- Establish early diagnostic criteria separating oGVHD from other forms of DED (tear film, impression cytology, cytokines, genetic markers, optical biomarkers (optical coherence tomography or confocal microscopy))
- Develop efficacy outcome measures that can be used in oGVHD-specific clinical trials to assess response to specific interventions
- Conduct eye-targeted studies, for example: step down vs step up treatment
- Evaluate systemic treatment options with regard to efficacy in oGVHD
- Study animal models for oGVHD to identify therapeutic targets and test drug candidates and studies of functional connections between organ-systems of cGVHD



Associated Manifestations of cGVHD



- Immune-mediated disorders not meeting the NIH criteria frequently occur either associated with NIH defined cGVHD or isolated – typically not captured in a structured way – incidence and risk factors mainly unknown
 - Well characterized CNS manifestations are rare but neurocognitive impairment frequent (70%) with attention impairment being more prominent in cGVHD (role of cGVHD?)
 - Peripheral Neuropathies are frequent and often associated with cGVHD (role of cGVHD?)
 - Endothelial damage is a frequent manifestation of GVHD across organs and cardiovascular mortality is one of the leading causes of mortality (role of cGVHD?)
- Perform appropriate natural history trials to capture and characterize these manifestations



Trial design issues in cGVHD

- Develop and apply appropriate endpoints depending on organs of interest and time of the disease course (CR/PR may not apply at fibrotic manifestations)
- If aim is stable disease the trajectory of disease prior to inclusion is required
- Non-randomized trials may benefit from historical controls or prior trajectory
- Very rare entities (N of 1 trials) require a standardized approach (incl. cross over) to permit later joint analyses
- Multiple agents may be evaluated within efficacy trials applying a futility or/and selection design



Summary of recommendations



1. Phenotype cGVHD within cohort studies, to describe incidence, predictive factors, mechanisms of organ damage, and natural history of highly morbid conditions applying common definitions and research sample collections.
2. Develop new approaches for early identification and treatment of highly morbid forms of cGVHD, incl. biologically targeted treatments, with a special focus on prevention and treatment of **fibrotic** changes.
3. Establish primary endpoints for clinical trials in relationship to the time point of intervention (early versus late). Other endpoints, such as lack of progression and improvement in functioning or quality of life, may be realistic endpoints for clinical trials of highly morbid manifestations. Explore novel trial designs for small populations.



Commentator

Open issues

- Reproducible response parameters for advanced disease
- Organ specific PROMs in organ specific trials
- Topical and supportive care options (QoL)
- Role of nutrition & microbiome
- Sorting the systemic and targeted effects in multiple organs
- Age, racial and ethnic minorities effects in clinical trials



NATIONAL CANCER INSTITUTE

Panel Q and A





Audience Discussion

