PATIENT-REPORTED SYMPTOM BURDEN OF CHRONIC GRAFT VERSUS HOST DISEASE: A SYSTEMATIC LITERATURE REVIEW

Marcell Csanádi[1], Szabolcs Farkas-Ráduly[2], Blanca Gros[3], Trevor Bacon[4], Christoph Tapprich[5], Jeremiah J Trudeau[6], Tamas Ágh[1*]

[1]Syreon Research Institute, Hungary; [2]Syreon Research Romania, Romania;
[3]Janssen-Cilag S.A., Spain, [4]Janssen Sciences Ireland UC, Ireland; [5]Janssen EMEA Medical Affairs, Germany; [6]Janssen Global Services LLC, USA
*presenting author

INTRODUCTION

- Chronic graft versus host disease (cGVHD) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT). It is an immune-mediated syndrome causing high morbidity by involving a wide range of organs (i.e., skin, mouth, eye, genital tract, gastrointestinal tract, liver, lung, joint/fascia and hematopoietic systems of bone marrow) [1].
- The importance of collecting data from the cGVHD patients about their symptoms, global severity scores, perception of disease activity and change, functional status, and quality of life using validated questionnaires received more attention in recent years [2]. These data can be collectively called patient-reported outcomes (PROs).
- The symptom burden is an important patient self-administered outcome of patients diagnosed with a specific disease. In case of cGVHD the assessment of the disease symptoms should be reflective of the multi-organ manifestations [3].
- According to the National Institute of Health (NIH) Consensus Guidelines, cGVHD patients should score their perceptions of overall chronic GVHD severity, overall severity of symptoms, and change in symptom severity on different validated scales [4].

OBJECTIVES

- **The objectives of this literature review were:**
  - **To collect and summarize published symptom related PRO data of cGVHD patients defined by the NIH 2005 or 2014 Consensus Guidelines [5,6];**
  - **To evaluate the association of patient reported symptom burden with a wide range of potentially relevant health outcomes in patients with cGVHD defined by the NIH 2005 or 2014 Consensus Guidelines [5,6].**

METHODOLOGY

- The literature search was conducted on November 26th, 2018 and it covered Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE databases. The search strategy was built up as a combination of subjects headings and 'free-text' terms related to the disease and PRO measures.
- The following exclusion criteria were applied during title and abstract screening conducted by two independent researchers: (1) no abstract is available; (2) not written in English; (3) editorial, letter, case report, review articles or systematic literature reviews; (4) not related to cGVHD; and (5) not reported any PRO data.
- Eligible articles were screened in full text. During full text screening the set of title and abstract exclusion criteria were extended by the following additional criterion: (6) cGVHD is not defined using the 2005 or 2014 NIH Consensus Criteria [5,6]
- Data from included studies were extracted by independent reviewers to a Microsoft (MS) Excel file.
- Quality assessment of the included studies was performed (by two reviewers per article) using the NIH Quality Assessment Tool for Controlled Clinical Trials/Observational Cohort and Cross-Sectional Studies [7].

RESULTS

- The literature search resulted in 1,211 found references. After deduplication, 892 studies underwent title and abstract screening of which 691 studies were excluded. After the review of the remaining 201 potentially relevant full text articles, 38 studies were identified, which reported data on symptom burden in cGVHD patients.
- The references of the full list of included articles can be found on the following link: http://syreon.eu/evcms_medias/upload/files/cgvhd_pro_symptom_burden_poster_reference_list__002_.pdf

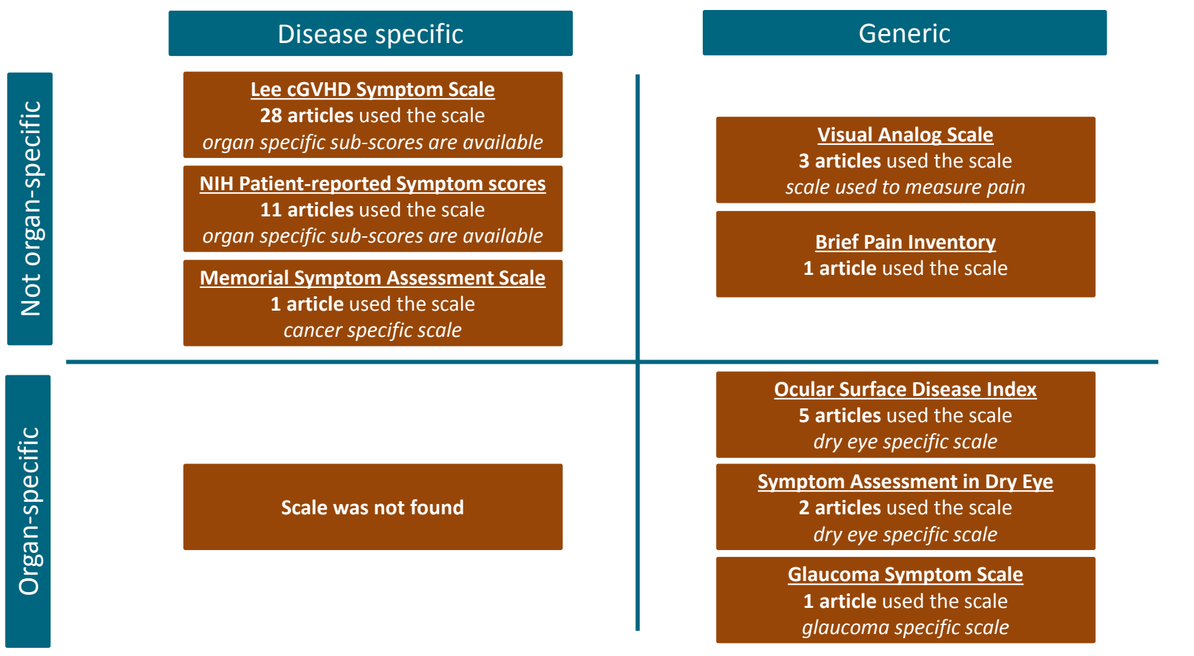
General characteristics of the included studies

- Different study designs were applied, the most frequently used were prospective (n=18) and cross-sectional cohort study (n=10). There were 4 retrospective studies, 5 phase II clinical trials and 1 randomized double-blind clinical trial.
- Out of the 38 included studies 35 used the 2005 and 3 used the 2014 NIH Consensus Criteria to define cGVHD. The number of involved cGVHD patients ranged from 19 to 584.
- The majority (n=28) of the studies were conducted in the USA. There were 2 studies from Italy, 2 studies from France, 1 study from the UK, 1 study from Germany, 1 study from Brazil, 1 study from Turkey. In 1 case the study location was not reported and in 1 case the study was conducted in multiple countries.
- The symptom burden of oral and ocular cGVHD were investigated most frequently with 8-8 articles, respectively. The remaining organ-specific studies investigated the symptom burden of lung, skin and joint/fascia manifestations.

Instruments used to measure symptom burden of cGVHD patients

- The Lee cGVHD Symptom Scale was used most frequently by 28 studies.
- The NIH Patient-reported Symptom scores were used by 11 studies to assess the symptom burden related to the global severity of cGVHD, ocular, oral and skin organ involvement.
- Generic instruments were used by few studies: the Visual Analog Scale to assess pain and the Brief Pain Inventory
- Disease specific instruments included the Ocular Surface Disease Index and Symptom Assessment in Dry Eye for assessing dry eye, while the Glaucoma Symptom Scale was used to assess glaucoma symptoms. The cancer-specific Memorial Symptom Assessment Scale was also used by one study.
- The instruments used to measure symptom burden of cGVHD patients are summarized in the table below (**Figure 1**).

Figure 1. Summary of different instruments used to measure symptom burden of cGVHD patients



Symptom burden data about cGVHD patients measured by Lee cGVHD symptom scale

- The different types of data related to the Lee cGVHD Symptom Scale are summarized in the table below (**Figure 2**).
- Table 1 and Table 2 includes the results of those studies, where multivariate analysis was applied to investigate the symptom burden

Figure 2. Summary of data related to the measurement of symptom burden of cGVHD patients

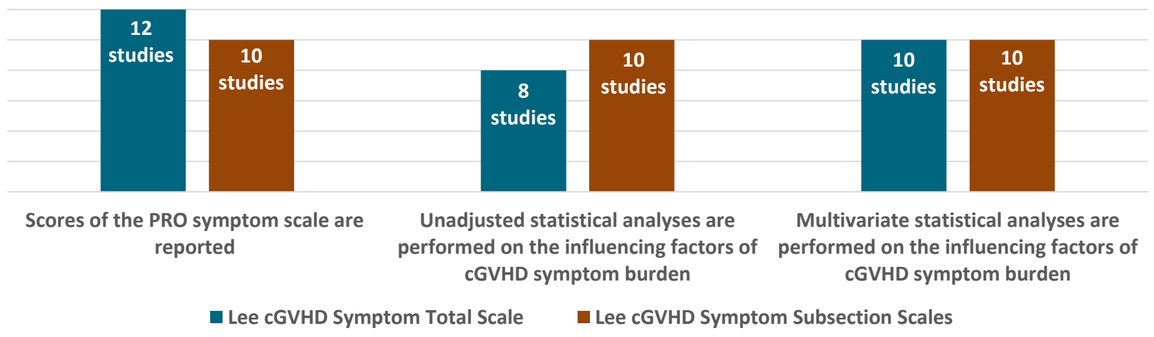


Table 1. Lee cGVHD Symptom Total Scale - Results of multivariate statistical analyses

Investigated influencing factors of symptom burden and the related key findings
Age *(El-Jawahri A et al., 2014)*
Age was **not a significant predictor** of overall cGVHD symptom burden
Self-reported depression; Self-reported anxiety *(El-Jawahri A et al., 2018)*
Patients with self-reported depression and patients with self-reported anxiety symptoms had **worse symptom burden**
Income level; Ability to return to work *(Hamilton BK et al., 2018)*
Higher income was significantly associated with **better symptom burden**
The „ability to return to work" was significantly associated with **better symptom burden**
Overall response to systematic treatment; Use of prednisone treatment *(Inamoto Y et al., 2012)*
Incident cGVHD cases: responders (partial + overall pooled) had **significant improvement** in the symptom burden
Prevalent cGVHD cases: responders (partial + overall pooled) had **no significant improvement** in the symptom burden
Prednisone treatment for cGVHD patients at 6 months was associated with **worse symptom burden**
Treatment with daily prednisone for cGVHD patients was associated with **worse symptom burden**
Clinician / Patient reported change in cGVHD symptoms *(Inamoto Y et al., 2014)*
Clinician reported improved disease symptoms were **not associated with significant changes** in symptom burden
Clinician reported worsening disease symptoms were **associated with significant changes** in symptom burden
Patient reported improved and worsening disease symptoms were **associated with significant changes** in symptom burden
Functional performance *(Mitchell SA et al., 2010)*
Better symptom burden was associated with better functional performance physical component summary of the SF-36
Clinical parameters of the lung *(Palmer J et al., 2014)*
Clinician defined NIH symptom-based lung scores were **correlated with the symptom burden**
NIH pulmonary function tests-based lung scores of 2 or 3 were **correlated with the symptom burden**
Different lung capacity categories were **not correlated with the symptom burden**
Clinical diagnosis of BOS did **not correlate with the symptom burden**
Involvement of the gastrointestinal tract *(Pidala J et al., 2013a)*
The clinician-reported esophageal cGVHD involvement was significantly associated with **worse symptom burden**
The overall gastrointestinal cGVHD involvement was significantly associated with **worse symptom burden**
Functional capacity *(Pidala J et al., 2013b)*
Shorter distance on the 2 minute walk test was associated with **worse symptom burden**
Involvement of the eyes *(Sun YC et al., 2015)*
Worse symptom burden was associated with ocular cGVHD involvement

cGVHD: chronic graft versus host disease; SF-36: Short Form (36); NIH: National Institute of Health; BOS: bronchiolitis oblitareans syndrome;

Table 2. Lee cGVHD Symptom subscales - Results of multivariate statistical analyses

Investigated influencing factors of symptom burden and the related key findings
cGVHD severity, personality features *(Herzberg PY et al., 2013)*
Higher cGVHD severity was **associated** with higher **energy** and **mental and emotional** subscale scores
Personality characteristics were **associated** with **energy** and **mental and emotional** subscale scores
Fatigue *(Im A et al., 2016)*
Fatigue was **associated** with higher scores on the **breathing** and on the **muscles and joints** subscales
Organ response to systematic treatment *(Inamoto Y et al, 2012)*
Incident cGVHD cases: organ response (partial + complete pooled) was **associated** with improved scores for the **skin, eyes and mouth**, and **eating and digestion** subscales
Prevalent cGVHD cases: organ response (partial + complete pooled) was **not significantly associated** with **any of the subscales**
Clinician / Patient reported change in cGVHD symptoms *(Inamoto Y et al., 2014)*
Clinician reported improved disease symptoms were **not associated** with the **muscles and joints** subscale
Clinician reported worsening disease symptoms were **associated** with the **muscles and joints** subscale
Patient reported improved and worsening disease symptoms were **associated** with in the **muscles and joints** subscale
Clinician / Patient reported change in skin symptoms *(Jacobsohn DA et al., 2012)*
The **skin** subscale showed **significant association** with clinician and patient reported worsening and improvement of the skin symptoms
Overall mortality; Non-relapse mortality *(Jacobsohn DA et al., 2012)*
A score greater than 15 in the **skin** subscale at enrollment was **associated** with increased OM and NRM
The improvement in the **skin** subscale at 6 months was **associated** with improved OM and NRM
The worsening **skin** subscale at 6 months was **not associated** with worse OM or NRM
The improvement in the **skin** subscale at 12 months was **not associated** with improved OM and NRM
The worsening **skin** subscale at 12 months was **not associated** with worse OM or NRM
Clinical parameters of the lung *(Palmer J et al., 2014)*
Clinician defined NIH symptom-based lung scores were **correlated** with the **breathing** subscale; NIH pulmonary function tests-based lung score of 2 was **correlated** with the **breathing** subscale; Different lung capacity categories were **not correlated** with the **breathing** subscale; Clinical diagnosis of BOS **correlated** with the **breathing** subscale
Overall survival; Non-relapse mortality *(Palmer J et al., 2016)*
Improvements in **skin** symptom subscale were **associated** with better overall survival
Worsening in **skin** symptom subscale were **associated** with better NRM
Involvement of the gastrointestinal tract *(Pidala J et al., 2013a)*
Higher **eating and digestion** scores were **associated** with the involvement of esophageal, the involvement upper gastrointestinal tract and with the involvement lower gastrointestinal tract
Functional capacity *(Pidala J et al., 2013b)*
Shorter 2 minute walk test was **associated** with higher scores on **skin**, **breathing**, and **energy** subscales
Hand grip strength was **not associated** with higher scores on **any of the subscales**
Clinician / Patient reported change in mouth symptoms *(Treister N et al., 2013)*
Patient-perceived change in oral cGVHD was **correlated** with change in the **mouth** subscale
Clinician-perceived change in oral cGVHD did **not correlate** with change in the **mouth** subscale

cGVHD: chronic graft versus host disease; NIH: National Institute of Health; BOS: bronchiolitis oblitareans syndrome; OM: overall mortality; NRM: non-relapse mortality

CONCLUSION

- **The patient-reported symptom burden among patients diagnosed with cGVHD by NIH Consensus Criteria was comprehensively assessed in the literature using different validated scales.**
- **The Lee cGVHD Symptom Scale was the most frequently used instrument in the reviewed studies. This reflects on the recommendation by the NIH Consensus Criteria to use the scale to assess patient-reported symptom burden of cGVHD.**
- **A wide range of factors have been investigated to better understand the association of cGVHD patient-reported symptom burden with other patient- or clinician-reported features. Still, we identified some important evidence gaps in the literature:**
  - Although the skin subscale of the Lee cGVHD Symptom Scale was used for predicting hard clinical endpoints, we did not identify any study that investigated the total score of the scale or other subscale in this regard
  - Association between Lee cGVHD Symptom Scale scores and quality of life measures was not investigated in the included studies.
  - Although some other PRO instruments (i.e. NIH Patient-reported Symptom scores) were also used for predicting hard clinical endpoints (data not shown on the poster), this was also limited to a particular organ involvement (i.e. skin).
  - The NIH Patient-reported Symptom scores were used to predict patients' quality of life, however they were limited to a particular organ involvement (i.e. mouth).
- **It is recommended to replicate this research in the future to investigate whether these gaps will be answered in the upcoming studies on cGVHD.**

REFERENCES

1. Socie G and Ritz J. (2014) Current issues in chronic graft-versus-host disease. Blood. 124:374-84.
2. Krupski C and Jagasia M. (2015) Quality of Life in the Chronic GVHD Consortium Cohort: Lessons Learned and the Long Road Ahead. Curr Hematol Malig Rep. 10(3):183-91.
3. Lee S et al., (2002). Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 8(8):444-52.
4. Pavletic SZ et al. (2006) Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant. 12(3):252-66.
5. Filipovich AH et al. (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 11:945-56.
6. Jagasia MH et al. (2015) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and staging working group report. Biol Blood Marrow Transplant. 21:389-401.
7. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

DISCLOSURES & ACKNOWLEDGMENTS

Syreon Research Institute received a grant from Janssen Research & Development, LLC to conduct this study.

Poster presented at ISPOR Europe 2019 Congress, November 4, 2019, Copenhagen, Denmark.

Sponsored by Janssen Research & Development, LLC.