Burden of hospitalizations and outpatient visits associated with moderate and severe acute graft-versus-host disease in Finland and Sweden: a real-world data study

Lorenzo Sabatelli1 · Mikko Keränen2 · Elisabet Viayna3 · Montserrat Roset3 · Nuria Lara3 · Daniel Thunström1 · Minja Pfeiffer1 · Malin Nicklasson4 · Maija Itälä-Remes5

Received: 31 August 2021 / Accepted: 12 February 2022 / Published online: 2 March 2022
© The Author(s) 2022

Abstract
Purpose The aim of this study was to describe patient characteristics and quantify hospital stays and outpatient visits (H&OV) following diagnosis with moderate-to-severe acute graft-versus-host disease (aGVHD) in Finland and Sweden.

Methods A retrospective chart audit collected data from patient medical records of 3 specialized centers performing allogeneic hematopoietic stem cell transplantation (HSCT; Finland, n = 2; Sweden, n = 1). Eligible patients received allogeneic HSCT (January 1, 2016–June 30, 2017) from any donor source, were diagnosed with grade II–IV aGVHD (MAGIC or modified Glucksberg criteria) at any time from transplantation to 12 months before data collection, and were ≥ 18 years old at diagnosis. Criteria for comparing patients graded with modified Glucksberg and MAGIC severity scales were defined.

Results Fifty-five patients (Finland, n = 45; Sweden, n = 10) were included. Myeloablative conditioning was the most common conditioning regimen (81.8%); immunosuppression regimens were based on combinations of methotrexate (96.4%), in vivo T-cell depletion (80.0%), cyclosporine (63.6%), mycophenolate (40.0%), and tacrolimus (34.5%). Sixteen patients (29.1%) developed grade III/IV aGVHD; skin was the most common organ involved (80.0%). Most patients required ≥ 1 hospital stay (89.1%; median of 2 hospitalizations per patient); 7 patients (14.3%) required admission to an intensive care unit. Median hospitalization duration from HSCT to discharge was 26 days. Most patients also required outpatient or emergency department visits (90.9%). Subgroup analyses showed longer hospital stays for patients receiving multiple lines of therapy; no clear differences in H&OV were observed between prophylactic regimens.

Conclusion Based on this retrospective study, moderate-to-severe aGVHD is associated with considerable healthcare resource utilization in Finland and Sweden, particularly in patients who received multiple lines of therapy.

Keywords Acute graft-versus-host disease · Outpatient · Hospitalization · Real-world data · Severity grades · MAGIC · Glucksberg

Abbreviations
aGVHD Acute graft-versus-host disease
ALL Acute lymphocytic leukemia
AML Acute myeloid leukemia
ATG Antithymocyte globulin
CMV Cytomegalovirus
DRI Donor lymphocyte infusion
DRI Disease risk index
EBMT European Society for Blood and Marrow Transplantation
EBMT–NIH-CIBMTR European Society for Blood and Marrow Transplantation and National Institutes of Health Center for International Blood and Marrow Transplant Research
eCRFs Electronic case report forms
GI Gastrointestinal
GVHD Graft-versus-host disease
H&OV Hospital stays and outpatient visits
HLA Human leukocyte antigen

Footnotes
1 Incyte Biosciences International Sàrl, Rue Docteur Yersin 10, 1110 Morges, Switzerland
2 Helsinki University Hospital, Helsinki, Finland
3 IQVIA Real World Solutions, Barcelona, Spain
4 Department of Hematology and Coagulation, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
5 Turku University Hospital, Turku, Finland

The authors declare no conflict of interest.

© The Author(s) 2022

Supportive Care in Cancer (2022) 30:5125–5135
https://doi.org/10.1007/s00520-022-06915-9

Check for updates

Original Article

Supportive Care in Cancer
Introduction

Graft-versus-host disease (GVHD), a serious complication of allogeneic hematopoietic stem cell transplantation (HSCT), is a clinical syndrome caused by the response of alloreactive donor T cells to histocompatibility antigens expressed on tissues of the transplant recipient [1, 2]. The European Society for Blood and Marrow Transplantation and National Institutes of Health Center for International Blood and Marrow Transplant Research (EBMT–NIH-CIBMTR) joint classification for acute GVHD (aGVHD) includes classic aGVHD, defined by the occurrence of aGVHD manifestations within 100 days after transplantation or donor lymphocyte infusion (DLI), as well as persistent, recurrent, or late-onset forms of aGVHD, which occur beyond 100 days posttransplantation or after DLI [3, 4]. Clinical manifestations of aGVHD typically develop in the skin, gastrointestinal (GI) tract, or liver, leading to erythema, maculopapular rash, nausea, vomiting, anorexia, diarrhea, ileus, increase of liver transaminases, or cholestatic hyperbilirubinemia; severity of aGVHD is determined by the extent of involvement of these principal target organs [2, 4, 5].

Despite routine use of prophylactic regimens, aGVHD occurs in 30 to 60% of patients undergoing allogeneic HSCT [6, 7]. Corticosteroids are currently a standard of care for first-line therapy for aGVHD. However, up to 60% of patients do not respond adequately to steroids [8–11]. For these patients, a choice of second-line therapy remains controversial.

Acute GVHD is a leading cause of post-HSCT nonrelapse mortality and has been previously associated with increased hospital stays and outpatient visits (H&OV). However, real-world data (RWD) for aGVHD-related outcomes of transplanted patients and the associated H&OV are scarce and partly outdated. A retrospective analysis of patients undergoing allogeneic HSCT between 2006 and 2009 in the UK showed significantly higher rates of hospital readmission leading to higher costs for patients with GVHD compared to those without [12]. Furthermore, retrospective analyses from large US hospitals have shown that patients who developed aGVHD, especially in the subgroups of steroid-refractory or high-risk disease, had significantly longer hospital stays, higher rates of hospital readmissions, higher intensive care unit (ICU) admission rates, greater costs, and increased risk of mortality compared with those who did not develop GVHD [13–15].

Currently, there are only a few studies reporting aGVHD-related morbidity and mortality or H&OV-related healthcare resource utilization in contemporary European transplantation centers [16, 17]; thus, RWD analyses from additional sample populations in European countries are needed to more precisely determine GVHD-related burden. The aim of this study was to describe the clinical presentation, prophylactic treatments, hospitalizations, and outpatient visits among patients who developed moderate or severe aGVHD.

Methods

Study design and patients

This was a noninterventional, retrospective chart review study that originally planned to enroll patients in 4 European countries (Germany, Italy, Sweden, and Finland); however, due to the sponsor’s decision to reduce the scope of the study for resource considerations, study data were ultimately retrieved from 2 sites in Finland (Turku and Helsinki) and one site in Sweden (Gothenburg). The sites were specialized centers belonging to the EBMT that routinely perform allogeneic HSCT. Patients were included retrospectively and consecutively, starting with those who received HSCT on June 30, 2017, and subsequently developed aGVHD, and working backward recruiting those who had received HSCT until January 1, 2016, or until the target sample size of approximately 4 to 25 patients per center had been reached, whichever occurred first (Online Resource 1). Patient charts were reviewed from the index date (date of allogeneic HSCT) until the day of data collection, death, or loss to follow-up, whichever occurred first.

Study eligibility criteria included receipt of a first allogeneic HSCT between January 1, 2016, and June 30, 2017, from any donor source using bone marrow, peripheral blood stem cells (PBSCs), or umbilical cord blood; diagnosis of grade II–IV aGVHD based on Mount Sinai Acute GVHD International Consortium (MAGIC) criteria [18] (or alternatively, a II–IV severity grade per the Glucksberg Severity Index or the Keystone Criteria [19], or grade B–D according
to International Blood and Marrow Transplant Research (IBMTR criteria [20]) any time from transplantation to 12 months before data collection; and age ≥18 years at the time of aGVHD diagnosis. Only patients with complete clinical records containing the main clinical characteristics related to the original disease requiring allogeneic HSCT and clinical information on aGVHD presentation and treatment were included. Exclusion criteria included receipt of >1 HSCT; participation in a GVHD prophylaxis trial with a primary completion date later than December 31, 2018 (to ensure that trial results would be available by the time of patient enrollment), or in any GVHD treatment trial at any point during the data collection period (i.e., January 2016 until the time of data collection, death, or loss to follow-up); disease progression before the first aGVHD episode; or aGVHD following DLI.

Data collection

Patient data were collected from patient medical records and entered into electronic case report forms (eCRFs). Data from the eCRFs corresponding to eligibility criteria were regularly reviewed to ensure inclusion of eligible patients only and for consistency. Data on patient demographics, transplant characteristics, disease risk index (DRI; an index for stratification of patients undergoing HSCT by disease risk) [21, 22], aGVHD clinical characteristics, treatments, outcomes, and H&OV (hospitalizations/inpatient admissions and outpatient and emergency department visits) were collected. For each patient, length of hospitalizations and ICU stays were calculated based on date of admission and discharge; only hospitalizations and ICU stays that took place during or after aGVHD diagnosis were considered. If a patient was in the hospital at the time of aGVHD diagnosis, the ongoing hospitalization episode was included in the analysis, but any days spent in the hospital before the diagnosis were not considered.

Transplant conditioning regimens were recorded and classified as myeloablative conditioning (MAC), reduced-intensity conditioning (RIC), and sequential conditioning. Prophylactic regimen categories included ex vivo T-cell depletion, in vivo T-cell depletion (antithymocyte globulin [ATG], alemtuzumab, other), cyclosporine, steroid, tacrolimus, posttransplant cyclophosphamide, methotrexate, mycophenolate, sirolimus, and other. Data were collected on the number of treatment lines initiated.

Statistical analyses

All disease diagnoses (e.g., comorbidities) and medical procedure terms were recorded and coded using the Medical Dictionary for Regulatory Activities. All computations were performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA). To ensure comparability across different grading systems, aGVHD severity was compared across scales and based on extent of skin, liver, and GI involvement, with grades II–IV (MAGIC and modified Glucksberg/Key- stone criteria) defined as skin stage ≥3 and/or liver ≥1 and/or GI ≥1, and grades B–D (IBMTR criteria) defined as skin stage ≥2 and/or liver ≥1 and/or GI ≥1 (Online Resources 2A and B) [4]. Mapping rules to compare patients graded per MAGIC criteria with those graded using a different scale were derived from grade and organ score definitions specific to each scale (Online Resources 3 and 4).

Data were summarized using descriptive statistics. Continuous variables were reported using mean, median, standard deviation, interquartile range, minimum, and maximum. Categorical values were summarized as number and proportion of the total study population and by subgroups, where appropriate. Missing values were reported for categorical and continuous values but were excluded to calculate percentages of patients. Although the study has a descriptive design, the probability that subgroup differences in outcomes (large or larger than observed) could have occurred under the null hypothesis of no difference was calculated using P-values, if ≥10 patients per category were reached. No P-value threshold was prespecified or used to draw conclusions. The chi-squared test was used to compare categorical variables, and the nonparametric Kruskal–Wallis test was used to compare continuous variables.

Subgroup analyses were conducted to evaluate differences in H&OV (e.g., number and length of hospitalizations, reasons for hospitalizations, number and length of ICU admissions, number of and reasons for emergency department and outpatient visits) based on number of treatment lines (1 vs ≥2 lines of treatment) and type of prophylactic regimens received (1 tacrolimus plus mycophenolate, in vivo T-cell depletion and methotrexate; 2 in vivo T-cell depletion plus methotrexate and cyclosporine; 3 methotrexate plus cyclosporine; or 4 other). A change in treatment lines was defined as replacement of an anti-aGVHD drug with another anti-aGVHD drug and/or addition of an anti-aGVHD drug to the previous regimen.

Results

Patient characteristics

Overall, there were approximately 50 patients in Finland and 80 patients in Sweden who developed grade II to IV aGVHD after HSCT from January 1, 2016, to June 30, 2017 (calculation based on EBMT data [23]). A total of 55 patients (Finland, n=45; Sweden, n=10) were treated in participating centers, met inclusion criteria, and were therefore included in this study (Table 1). Acute myeloid leukemia
Table 1  Patient demographics and clinical characteristics at transplant

| Characteristic                                      | Finland (n = 45) | Sweden (n = 10) | Total (N = 55) |
|----------------------------------------------------|------------------|-----------------|----------------|
| Age at HSCT, y                                      |                  |                 |                |
| Median (range)                                      | 54.0 (21.0–66.0) | 44.5 (20.0–71.0) | 51.0 (20.0–71.0) |
| Age at aGVHD diagnosis, y                           |                  |                 |                |
| Median (range)                                      | 54.0 (21.0–66.0) | 44.5 (20.0–71.0) | 51.0 (20.0–71.0) |
| Male, n (%)                                         | 25 (55.6)        | 5 (50.0)        | 30 (54.5)      |
| Primary disease diagnosis, n (%)                   |                  |                 |                |
| AML                                                | 16 (35.6)        | 3 (30.0)        | 19 (34.5)      |
| Multiple myeloma                                    | 8 (17.8)         | 0               | 8 (14.5)       |
| B-cell lymphoma (NHL)                               | 3 (6.7)          | 2 (20.0)        | 5 (9.1)        |
| MDS                                                | 4 (8.9)          | 0               | 4 (7.3)        |
| MPN                                                | 4 (8.9)          | 1 (10.0)        | 5 (9.1)        |
| ALL                                                | 3 (6.7)          | 1 (10.0)        | 4 (7.3)        |
| Hodgkin lymphoma                                    | 3 (6.7)          | 1 (10.0)        | 4 (7.3)        |
| Othera                                             | 3 (6.7)          | 2 (20.0)        | 5 (9.1)        |
| Stage at transplant, n (%)                          |                  |                 |                |
| Complete remission                                  | 29 (64.4)        | 5 (50.0)        | 34 (61.8)      |
| Partial remission                                   | 9 (20.0)         | 3 (30.0)        | 12 (21.8)      |
| Active relapse or PD                                | 5 (11.1)         | 1 (10.0)        | 6 (10.9)       |
| Untreated                                           | 2 (4.4)          | 1 (10.0)        | 3 (5.5)        |
| DRI,b n (%)                                         |                  |                 |                |
| Low                                                | 8 (17.8)         | 2 (20.0)        | 10 (18.2)      |
| Intermediate                                       | 21 (46.7)        | 6 (60.0)        | 27 (49.1)      |
| High                                               | 9 (20.0)         | 2 (20.0)        | 11 (20.0)      |
| Very high                                          | 1 (2.2)          | 0               | 1 (1.8)        |
| Unknown                                            | 6 (13.3)         | 0               | 6 (10.9)       |
| Stem cell source, n (%)                             |                  |                 |                |
| PBSC                                               | 45 (100.0)       | 8 (80.0)        | 53 (96.4)      |
| Bone marrow                                        | 0               | 2 (20.0)        | 2 (3.6)        |
| Related donor, n (%)                                | 8 (17.8)         | 5 (50.0)        | 13 (23.6)      |
| Fully HLA-matched twin                             | 5 (62.5)         | 0               | 5 (38.5)       |
| HLA-mismatched related donor                       | 0               | 1 (20.0)        | 1 (7.7)        |
| HLA-matched related donor                          | 3 (37.5)         | 4 (80.0)        | 7 (53.8)       |
| Unrelated donor, n (%)                             | 37 (82.2)        | 5 (50.0)        | 42 (76.4)      |
| HLA matched                                        | 35 (94.6)        | 5 (100.0)       | 40 (95.2)      |
| HLA mismatched                                     | 2 (5.4)          | 0               | 2 (4.8)        |
| Recipient serologic CMV-positive status, n (%)      | 29 (64.4)        | 8 (80.0)        | 37 (67.3)      |
| Maximum level of chimerism, n (%)                  |                  |                 |                |
| Full donor chimerism                                | 26 (57.8)        | 10 (100.0)      | 36 (65.5)      |
| Mixed or partial chimerism after reaching full chimerismc | 5 (19.2) | 7 (70.0) | 12 (33.3) |
| Unknown                                            | 19 (42.2)        | 0               | 19 (34.5)      |
| aGVHD organ symptom involvement, n (%)             |                  |                 |                |
| Skin                                               | 37 (82.2)        | 7 (70.0)        | 44 (80.0)      |
| Lower GI tract                                      | 23 (51.1)        | 4 (40.0)        | 27 (49.1)      |
| Liver                                              | 11 (24.4)        | 1 (10.0)        | 12 (21.8)      |
| Upper GI tract                                      | 10 (22.2)        | 0               | 10 (18.2)      |

aGVHD, acute graft-versus-host disease; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; DRI, disease risk index; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cell; PD, progressive disease. aOther includes chronic myeloid leukemia (n = 2), blastic plasmacytoid dendritic cell neoplasia, chronic myelomonocytic leukemia, and T-cell lymphoma (n = 1 each). bDRI determined as described in Armand P, et al. Blood. 2014;123(23):3664–3671. cAmong patients who reached full chimerism (Finland, n = 26; Sweden, n = 10; total, n = 36)

 Springer
was the most common indication for HSCT \((n = 19 \ [34.5\%])\), followed by multiple myeloma \((n = 8 \ [14.5\%])\). At the time of HSCT, most patients were in complete \((n = 34 \ [61.8\%])\) or partial \((n = 12 \ [21.8\%])\) remission, and the most common DRI was intermediate \((n = 27 \ [49.1\%])\). Most donors were unrelated \((n = 42 \ [76.4\%])\), and of these, only 2 patients \(4.8\%\) received a human leukocyte antigen-mismatched graft. Most patients received a PBSC graft \((n = 53 \ [96.4\%])\). All patients for whom chimerism was determined \((n = 36)\) reached full donor chimerism as their maximum level of chimerism.

**Transplant conditioning regimen and aGVHD prophylaxis**

Myeloablative conditioning was the most common transplant conditioning regimen and was used in 45 transplants \(81.8\%\), followed by RIC in 9 transplants \(16.4\%\); Fig. 1A.

---

**Fig. 1** Transplant conditioning regimen and aGVHD prophylaxis. **A** Type of conditioning regimen used, by country and overall. **B** Specific conditioning regimens by category (MAC or RIC). **C** aGVHD prophylaxis used by country. aGVHD, acute graft-versus-host disease; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation.
Most patients received fludarabine-based conditioning \((n = 41/55 [74.5\%])\), and 15 (27.3\%) patients received total body irradiation (TBI)-based conditioning (Fig. 1B). Fludarabine was most frequently administered alone \((n = 26/41; 63.4\%\)) , followed by combinations with TBI \((n = 8/41 [19.5\%]\)), thiotepa \((n = 4/41 [thiotepa alone, n = 1; thiotepa plus cyclophosphamide, n = 3]; 9.8\%)\), treosulfan \((n = 2/41 [4.9\%]\)), or melphalan \((n = 1/41 [2.4\%]\)). Busulfan administered over 3 or 4 days was defined as MAC, and over 2 days as RIC (the total of daily doses was the same). Treosulfan was administered over 3 days; a daily dose of 14 g/m\(^2\) was classified as MAC, and a daily dose of 10 g/m\(^2\) as RIC.

Immunosuppression was mainly based on the calcineurin inhibitors cyclosporine \((n = 35/55 [63.6\%]\)) and tacrolimus \((n = 19/55 [34.5\%]\)). Short-course methotrexate was used in almost all transplants \((n = 53/55 [96.4\%]\)), and a majority of patients also received ATG as in vivo T-cell depletion \((n = 44/55 [80.0\%]\)). Mycophenolate mofetil was frequently added to the combination \((n = 22/55 [40.0\%]\); Fig. 1C).

The most frequent prophylaxis combination was cyclosporine, methotrexate, and ATG \((n = 20/55 [36.4\%]\)) , followed by tacrolimus, methotrexate, ATG, and mycophenolate \((n = 14/55 [25.5\%]\)) and cyclosporine with methotrexate \((n = 7/55 [12.7\%]\)).

### Acute GVHD severity and organ symptom involvement

The scales used for grading aGVHD severity across the 3 participating centers were MAGIC \((n = 29/55 [52.7\%]\)) or modified Glucksberg \((n = 26/55 [47.3\%]\); Online Resource 5). Thirty-nine patients \((70.9\%)\) and 16 patients \((29.1\%)\) developed grade II and grades III/IV aGVHD, respectively. Skin was the most common organ involved \((n = 44/55 [80.0\%]\) , followed by the lower GI tract \((n = 27/55 [49.1\%]\)), liver \((n = 12/55 [21.8\%]\)), and upper GI tract \((n = 10/55 [18.2\%]\); Table 1).

### Nonpharmacologic H&OV since aGVHD diagnosis

Most patients with aGVHD \((n = 49/55 [89.1\%]\)) required at least one hospitalization period, primarily due to aGVHD \((n = 32/49 [65.3\%]\) or infections/infestations \((n = 22/49 [44.9\%]\); Fig. 2). Median (range) number of hospitalization periods per patient was 2.0 (0.0–10.0). Seven patients \((n = 7/49 [14.3\%]\) required admission to an ICU (Fig. 2). From the date of HSCT to discharge during the initial transplant period, the median duration of hospitalization was 26.0 days (Table 2), and nearly half of all hospitalizations lasted >7 days \((n = 72/158 [45.6\%]\); Online Resource 6). Mean (SD) days spent in the hospital and ICU following aGVHD grade II–IV diagnosis per 100 days of observation were 17.9 (31.4) and 0.7 (2.7), respectively (Table 2). In addition, most patients required an outpatient or emergency department visit following aGVHD grade II–IV diagnosis \((n = 50/55 [90.9\%]\); Fig. 2). On average, patients required a mean (SD) 11.7 (11.1) outpatient and 0.3 (0.6) emergency visits per year (Table 2).
Subgroup analyses

A subgroup analysis evaluating H&OV by number of treatment lines for aGVHD demonstrated similar rates of hospitalization between patients who received one treatment line (n = 22/24 [91.7%]) and those who needed at least 2 treatment lines (n = 27/31 [87.1%]). Patients who received at least 2 lines of therapy had a median hospitalization duration of 6.1 days per 100 patient-days, and those who received only one treatment line had 1.9 days (≥ 2 lines vs 1 line, *P* = 0.03; Table 3). Median number of hospitalization periods per patient and median number of days at ICU per 100 patient-days were the same between patients who received ≥ 2 lines or 1 line of treatment. The proportion of the study population requiring outpatient or emergency department visits was 87.1% among patients with ≥ 2 lines of prior treatment and 95.8% among those receiving only one prior line of treatment. The mean number of outpatient visits per patient per year was similar for the 2 subgroups (≥ 2 lines, 11.4; 1 line, 12.0; *P* = 0.16). Mean number of emergency department visits per patient-year was two-fold higher for patients who received only 1 line of treatment compared with those receiving 2 or more lines (≥ 2 lines, 0.2 visits/patient-year; 1 line, 0.4 visits/patient-year; *P* = 0.16); however, it cannot be excluded that this may be due only to chance.

When H&OV was assessed by prophylactic regimen categories, the lowest rate of hospitalization was observed among patients who received tacrolimus plus mycophenolate, in vivo T-cell depletion, and methotrexate (71.4% vs 100.0% for in vivo T-cell depletion plus methotrexate and cyclosporine, 100.0% for methotrexate plus cyclosporine, and 85.7% for other regimens). Patients who received tacrolimus plus mycophenolate, in vivo T-cell depletion, and methotrexate also spent considerably less (about half as many) days in the hospital on average (9.8 per 100 patient-days) compared with other treatment regimens. However, it cannot be ruled out that the observed differences may be due only to chance (Table 4).

Mortality rates since aGVHD development

At 6 months after aGVHD diagnosis, mortality rates in Finland and Sweden were 17.8% (n = 8) and 10.0% (n = 1), respectively. At 12 months, the mortality rates were 17.8% (n = 8) and 40.0% (n = 4).

Discussion

The present study provides a detailed description of the clinical characteristics and aGVHD-related H&OV of patients who developed aGVHD after allogeneic HSCT. These RWD were collected from 2 reference transplantation centers in Finland and one in Sweden. Owing to data availability, precise coverage of the Swedish population was unknown because exact estimates were not available; however, the study had a high coverage in the Finnish population, with 80 to 90% of nationwide eligible patients being included in this chart review study [23].
Although fewer than 30% of patients in the study presented with grade III or IV aGVHD, nearly 90% of patients required hospitalization. Overall, patients were hospitalized for a median of 26 days after a diagnosis of aGVHD and required more than 10 outpatient or emergency department visits per year. It should be noted that the hospitalization numbers in Gothenburg (Sweden) were higher than those reported in the 2 Finnish sites; one possible reason for this discrepancy is that it is standard at Gothenburg to call for multiple follow-up visits during the first few months after HSCT, with additional visits required following aGVHD diagnosis, which may result in hospital admissions. When stratified by treatment lines, patients who received at least 2 treatment lines had a longer hospital stay compared with those who received only one treatment line, although the rate of ICU admissions or length of treatment at ICU did not differ between these subgroups. With the exception of patients who received tacrolimus plus mycophenolate, in vivo T-cell depletion, and methotrexate, most prophylaxis regimens resulted in similar rates and duration of hospitalization or ICU admissions. These findings are consistent with those of the few other available studies conducted in the USA. An analysis of a large data set of hospital discharges showed that patients diagnosed with aGVHD had a significantly longer length of stay during initial hospitalization for HSCT versus those without aGVHD (31 vs 24 days, respectively) and were more likely to require ICU admission (40.6% vs 25.4%) [13]. Another national analysis of inpatient discharge records similarly showed an increased length of hospital stay among patients who developed aGVHD after HSCT versus those who did not (42.0 vs 26.0 days, respectively), as well as increased in-hospital mortality rates (16.2% vs 5.3%) [14].

These study’s findings show that, besides requiring considerable medical attention and arguably competing with other health conditions for limited healthcare resources, aGVHD is associated with a substantial financial burden for healthcare payers. In fact, based on the average cost of a day of hospitalization in Finland and Sweden, and on this study’s results, the average cost per patient for aGVHD-associated hospitalizations would amount to ~$25,000–$40,000.

### Table 3 Subgroup analysis of H&OV by prior lines of treatment

| Required hospitalization, n (%) | 1 line (n = 24) | ≥ 2 lines (n = 31) | P-value | Total (N = 55) |
|--------------------------------|----------------|-----------------|--------|----------------|
| Total number of hospitalizations | 22 (91.7) | 27 (87.1) | 49 (89.1) |
| Number of hospitalizations per patient | 55 | 104 | 159 |
| Mean (SD) | 2.3 (2.1) | 3.4 (3.0) | 0.55 | 2.9 (2.7) |
| Median (range) | 2.0 (0.0–10.0) | 2.0 (0.0–10.0) | 2.0 (0.0–10.0) |
| Duration of hospitalization per patient, days | | | |
| Mean (SD) | 22.2 (21.0) | 56.5 (56.8) | 41.3 (47.5) |
| Median (range) | 14.5 (0.0–81.0) | 35.0 (0.0–214.0) | 26.0 (0.0–214.0) |
| Days of hospitalization/100 patient-days | | | |
| Mean (SD) | 7.4 (19.8) | 26.4 (36.4) | 17.9 (31.4) |
| Median (range) | 1.9 (0.0–98.4) | 6.1 (0.0–100.0) | 3.9 (0.0–100.0) |
| Required admission to ICU, n (%) | 1 (4.5) | 6 (22.2) | 7 (14.3) |
| Duration of ICU stay per patient, days | | | |
| Mean (SD) | 0.6 (2.9) | 1.6 (5.2) | 1.1 (4.3) |
| Median (range) | 0.0 (0.0–14.0) | 0.0 (0.0–28.0) | 0.0 (0.0–28.0) |
| Days of ICU stay/100 patient-days | | | |
| Mean (SD) | 0.3 (1.7) | 1.0 (3.2) | 0.7 (2.7) |
| Median (range) | 0.0 (0.0–8.2) | 0.0 (0.0–13.5) | 0.0 (0.0–13.5) |
| Required outpatient or emergency department visit, n (%) | 23 (95.8) | 27 (87.1) | 50 (90.9) |
| Type of visit, n (%) | 23 (100.0) | 26 (96.3) | 49 (98.0) |
| Outpatient | | | |
| Emergency | 8 (34.8) | 5 (18.5) | 13 (26.0) |
| Missing | 0 | 1 (3.7) | 1 (2.0) |
| Number of outpatient visits per patient-year, mean (SD) | 12.0 (7.9) | 11.4 (13.2) | 11.7 (11.1) |
| Number of emergency department visits per patient-year, mean (SD) | 0.4 (0.7) | 0.2 (0.4) | 0.3 (0.6) |

H&OV, hospital stays and outpatient visits; ICU, intensive care unit. aPercentages calculated based on number of patients requiring hospitalization (1 line, n = 22; ≥ 2 lines, n = 27; total, n = 49). bIncludes patients with nonmissing visit type information (1 line, n = 24; ≥ 2 lines, n = 30; total, n = 54)
USD and $90,000 USD, respectively; similarly, based on the average cost of an outpatient visit in Finland and Sweden, the cost per patient for aGVHD-related outpatient visits per year amounts to $600–$1700 USD and $4700 USD, respectively (Online Resource 8). Although referring to a very different healthcare environment, these figures are overall comparable to those provided by a large US healthcare claims database study, which showed that the total healthcare costs incurred during a 1-year period following allogeneic HSCT were $100,000 USD higher for patients who developed aGVHD; additionally, hospital length of stay was nearly 3 weeks longer than for those without aGVHD [15]. Therefore, the present study supports and reinforces the findings of the few recent (US-based) studies, providing novel figures specific to the burden of H&OV in Finland and Sweden.

Limitations of this study include those typical of a retrospective chart review, such as the potential for medical charts being incomplete or inaccurate. These potential issues may have affected the calculations of H&OV and hospitalization durations, as well as information on treatment and prophylaxis. Nonetheless, the chart abstraction was conducted by qualified investigators from the enrolled centers familiar with the local ways of recording medical information. Variables collected were standard and clinically meaningful within acute GVHD populations, and specific information on variable definition was collected when needed. The use of an electronic case report made possible the implementation of an algorithm that performed consistency checks across the data filled in for each patient, reducing the risk of reporting errors. Finally, additional checks and triangulation of the clinical information were performed during the analyses.

The differences in aGVHD organ staging and grading systems (i.e., MAGIC vs modified Glucksberg), which could have an impact on the interpretation of results, were addressed by grouping and restaging modified Glucksberg cases using MAGIC criteria, instead of doing the opposite mapping (which would be affected by considerably higher uncertainty due to stage and grade definitions in the 2 scales) or naively comparing patients graded in MAGIC

---

**Table 4** Subgroup analysis of H&OV by prophylactic regimen

| Prophylaxis | Required hospitalization, n (%) | Total number of hospitalizations | Number of hospitalizations per patient | Duration of hospitalization per patient, days | Days of hospitalization/100 patient-days | Required admission to ICU, n (%) | Duration of ICU stay per patient, days | Days of ICU stay/100 patient-days |
|-------------|---------------------------------|---------------------------------|----------------------------------------|---------------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|-------------------------------------|
| Tacrolimus, mycophenolate, in vivo T-cell depletion, methotrexate (n = 14) | 10 (71.4) | 46 | Mean (SD) 3.3 (3.4) | Mean (SD) 33.1 (34.9) | 1 (10.0) | 0.4 (1.3) | 1.0 (3.6) | 0.0 (0.0–13.5) |
| In vivo T-cell depletion, methotrexate, cyclosporine (n = 20) | 20 (100.0) | 64 | Mean (SD) 3.2 (2.6) | Mean (SD) 51.9 (52.1) | 4 (20.0) | 2.7 (6.9) | 1.2 (3.3) | 0.0 (0.0–12.3) |
| Methotrexate, cyclosporine (n = 7) | 7 (100.0) | 15 | Mean (SD) 2.1 (1.9) | Mean (SD) 24.3 (21.3) | 1 (14.3) | 0.4 (1.1) | 0.1 (0.3) | 0.0 (0.0–0.8) |
| Other (n = 14) | 12 (85.7) | 34 | Median (range) 3.0 (0.0–10.0) | Median (range) 28.0 (0.0–104.0) | 1 (14.3) | Median (range) 0.0 (0.0–2.0) | Median (range) 3.1 (0.0–98.4) | Median (range) 0.0 (0.0–1.6) |

H&OV: hospital stays and outpatient visits; ICU: intensive care unit. aPercentages calculated based on number of patients requiring hospitalization (Tacrolimus, mycophenolate, in vivo T-cell depletion, methotrexate, n = 10; in vivo T-cell depletion, methotrexate, cyclosporine, n = 20; methotrexate, cyclosporine, n = 7; other, n = 12)
with patients graded in Glucksberg, as explained in Online Resource 7. In addition, the study was also limited by the small sample size, limiting statistical comparisons, especially at the subgroup level and particularly for Sweden, where information was only available from one hospital. Finally, variability existed between the Finland and Sweden data sets in terms of patient selection, which may have also affected the calculations and findings of the study.

In conclusion, findings from this study show that moderate to severe aGVHD is associated with considerable H&OV in Finland and Sweden, particularly in patients who received multiple lines of therapy. Larger follow-up studies across multiple regions, including prospective analyses, should be conducted to assess the generalizability of these findings to the aGVHD patient population as a whole.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-06915-9.

Acknowledgements The authors thank Emilio Sanchez and Eleonora Zonta (IQVIA; Barcelona, Spain) for their contribution to programming and data analysis. Writing assistance was provided by Jane Kovallevich, PhD, and Vicky Kanta, PhD, employees of ICON (Blue Bell, PA), and was funded by Incyte Corporation (Wilmington, DE).

Author contribution LS designed and performed research, analyzed and interpreted data, and wrote the manuscript. DT and MP analyzed and interpreted data and wrote the manuscript. MK, MN, and MI-R performed research, interpreted data, and wrote the manuscript. EV, MR, and NL designed research, performed statistical analyses, and wrote the manuscript.

Funding This study was funded by Incyte Corporation.

Data availability Access to individual patient-level data is not available for this study. Information on Incyte’s clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960

Code availability Not applicable.

Declarations

Ethics approval The study was conducted in accordance with the protocol, good pharmacoepidemiology practices, and the ethical principles embodied by the Declaration of Helsinki and applicable privacy laws. Institutional review boards/independent ethics committee reviewed and approved the study protocol before any patients were enrolled.

Consent to participate This was a retrospective chart review study using de-identified patient data; therefore, no consent was required.

Consent for publication This was a retrospective chart review study using de-identified patient data; therefore, no consent was required.

Conflicts of interest Lorenzo Sabatelli, Daniel Thunström, and Minja Pleiffer are employees and shareholders of Incyte Biosciences International. Mikko Keränen has provided consulting services for Novartis, Amgen, Janssen-Cilag, Pfizer, and Incyte Corporation; has an ownership interest in Iovance Biotherapeutics (IOVA); and has received honoraria from Accord Healthcare, Astellas, AbbVie, Amgen, and Takeda. Elisabet Viyanu, Montserrat Roset, and Nuria Lara are employees of IQVIA Real World Solutions. Malin Nicklasson and Maija Itäli-Remes report no conflicts of interest.

Disclosure of previous presentation Part of the results and methods of this manuscript were previously presented at Virtual ISPOR Europe 2020 (November 16–19, 2020).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Zeiser R, Blazar BR (2017) Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med 377:2167–2179. https://doi.org/10.1056/NEJMra1609337

2. Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373:1550–1561. https://doi.org/10.1016/S0140-6736(09)60237-3

3. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME (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(3):389-401.e381. https://doi.org/10.1016/j.bbmt.2014.12.001

4. Schoemans HM, Lee SJ, Ferrara JL, Wolf D, Levine JE, Schultz KR, Shaw BE, Flowers ME, Ruuuta T, Greinix H, Holler E, Basak G, Duarte RF, Pavletic SZ, EBMT Transplant Complications Working Party, EBMT–NIH–CIBMTR GvHD Task Force (2018) EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 53:1401–1415. https://doi.org/10.1038/s41409-018-0204-7

5. Krejci M, Kamelander J, Pospisil Z, Mayer J (2012) Kinetics of bilirubin and liver enzymes is useful for predicting of liver graft-versus-host disease. Neoplasma 59:264–268. https://doi.org/10.4149/neo_2012_034

6. Greco R, Lorentino F, Nitti R, Lupo Stanghellini MT, Giglio F, Clerici D, Xue E, Lazzari L, Piemontese S, Mastaglio S, Assanelli A, Marktel S, Corti C, Bernardi M, Ciceri F, Peccatori J (2019) Interleukin-6 as biomarker for acute GvHD and survival after allogeneic transplant with post-transplant cyclophosphamide. Front Immunol 10:2319. https://doi.org/10.3389/fimmu.2019.02319
10. Grubb WW, Huse S, Alam N, Dychter S, Wingard JR, Majhail NS, Berger A (2016) Economic burden of acute graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplant (HCT) for hematologic malignancies. Blood 128:1187. https://doi.org/10.1182/blood.V128.22.1187.1187
11. Svanh BM, Alvin O, Ringdén O, Gardulf A, Remberger M (2006) Costs of allogeneic hematopoietic stem cell transplantation. Transplantation 82:147–153. https://doi.org/10.1097/01.tp.0000226171.43943.d3
12. Svanh BM, Remberger M, Alvin O, Karlsson H, Ringdén O (2012) Increased costs after allogeneic haematopoietic SCT are associated with major complications and re-transplantation. Bone Marrow Transplant 47:706–715. https://doi.org/10.1038/bmt.2011.162
13. Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, Chanswangphuwan C, Efereba YA, Holler E, Lizotz M, Ordemann R, Qayed M, Hexner T, Shekhovtsova Z, Ferrara JL, Levine JE (2016) International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 22:4–10. https://doi.org/10.1016/j.bmt.2015.09.001
14. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995) 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 15:825–828
15. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, Cahn JY, Calderwood S, Gratwohl A, Socie G, Abeles MM, Sobocinski KA, Zhang M, Horowitz MM (1997) IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol 97:855–864. https://doi.org/10.1046/j.1365-2457.1997.1112925.x
16. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, Maziarz RT, Antin JH, Soiffer RJ, Weisdorf DJ, Rizzo JD, Horowitz MM, Saber W (2014) Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood 123:3664–3671. https://doi.org/10.1182/blood-2014-01-552984
17. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, Ritz J, Sorror ML, Lee SJ, Deeg HJ, Storer BE, Appelbaum FR, Antin JH, Soiffer RJ, Kim HT (2012) A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood 120:905–913. https://doi.org/10.1182/blood-2012-03-418202
18. European Society for Blood and Marrow Transplantation. Adult acute GVHD cases in Europe between 2014–2018 [unpublished data available from EBMT upon request, specific fees may apply]: 2019.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.