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RESEARCH

Ruxolitinib treatment outcomes in acute graft-versus-host disease (aGvHD) in a real-world setting in Finland

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Abstract

In Europe, ruxolitinib is the first approved treatment for corticosteroid-refractory/-dependent acute or chronic graft-versus-host disease (aGvHD/cGvHD). This retrospective, non-interventional study evaluated the real-world efficacy and safety of ruxolitinib in 56 adult aGvHD patients treated with ruxolitinib from January 2019 through August 2021 in Finland. The primary endpoint was best overall response rate (ORR) at any time. The main secondary endpoints were the time to response and loss of response, overall survival (OS), and corticosteroid discontinuation. The follow-up lasted until death/August 2022. The ORR was 91% (95% CI: 83.5–98.5; complete response [CR], 69.6%; partial response [PR], 21.4%). The median time to best response was 28 days (95% CI: 21–38). The median time to loss of response due to aGvHD progression, cGvHD, or a relapse-related death was 8.8 months (95% CI: 3.3–not reached). The most common cause of discontinuation was the achievement of response (64.3%). Two-thirds of the corticosteroid-treated patients discontinued corticosteroids before the end of follow-up; one-third were on a median dose of 0.2 mg/kg (IQR: 0.1–0.5) at the end of follow-up. The three-year OS was 64.1% (95% CI: 48.2–76.3). Ruxolitinib appears effective and safe in real-world practice. The presented data is in line with the results of clinical trials.

Keywords Acute graft-versus-host disease · Best overall response rate · Corticosteroid tapering · Response duration · Real-world evidence · Ruxolitinib

Introduction

Graft versus host disease (GvHD) is a life-threatening multisystemic disorder, which remains one of the main complications of allogeneic hematopoietic stem cell transplantations (allo-HSCT) [1, 2]. GvHD in its acute form (aGvHD), as well as in its chronic form (cGvHD), is associated with high morbidity and mortality [3–5]. Clinical features dictate whether GvHD is acute or chronic, or a subtype showing both acute and chronic disease characteristics [6, 7]. The incidence of aGvHD is 30–50%, with 10–15% of the patients developing severe or very severe, grade 3 to 4 aGvHD [8, 9].

Corticosteroids (CSs) are the first-line treatment for grade 2 to 4, but approximately half of the patients are steroid-refractory (SR-GvHD) and have a dismal prognosis [10–14]. Patients with SR-GvHD may benefit from ruxolitinib, the first approved treatment for patients aged 28 days and older with SR-aGvHD [15, 16]. Real-world evidence on the therapeutic management of GvHD with ruxolitinib is increasing [17–20]. Before the approval of ruxolitinib by the European Medicines Agency in 2022, no drug was licensed for the second-line treatment of GvHD in Europe. Accordingly, before 2022, there have been no guidelines for choosing a second-line treatment, and thus the choice has been made based on the clinical evaluation of each patient [10–12, 21–23].

The aim of this retrospective, non-interventional cohort study was to evaluate the real-world efficacy and safety of ruxolitinib in the treatment of aGvHD in Finland, based on

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a pre-approval data. The primary endpoint was best overall response rate (ORR). The secondary endpoints were time to response and loss of response as well as overall survival (OS) and CS discontinuation.

Materials and methods

Study design and permissions

This observational cohort study was conducted in accordance with the Declaration of Helsinki and the Act on Secondary Use of Health and Social Data 552/2019. The study protocol and data requests were approved by the Finnish Social and Health Data Permit Authority, Findata (THL/3757/14.02.00/2021). Due to the anonymity requirement of the data authority, results with low subject numbers were masked and it was ensured that the masked numbers cannot be deduced based on other available numbers.

Study population, data extraction, and study period

The study cohort was screened from medical records of Turku and Helsinki University Hospitals. The final cohort included all adult patients with aGvHD treated with ruxolitinib from Jan 2019 through Aug 2021. Ruxolitinib therapy was indicated for patients with either SR- or steroid-dependent (SD) aGvHD. However, some patients received ruxolitinib as part of the first-line therapy based on the clinician's discretion. For patients who received ruxolitinib treatment more than once, only the first exposure was considered in the analysis. All patients were followed until death or end of study (EOS), 31 August 2022, for OS and long-term utilization of CSs.

Demographic and clinical data was reviewed from the local medical records and linked with the national data on healthcare contacts and diagnoses (the Register of Primary Health Care Visits and the Care Register for Health Care, Finnish Institute for Health and Welfare, THL) and causes of deaths (Statistics Finland). Findata linked the data sets using personal identification numbers and provided pseudonymized data in a secure data environment where all the analyses were carried out.

Statistical analyses

Continuous demographic and clinical variables were reported with medians and interquartile ranges (IQR), categorical variables with number and proportion of patients per level. Grade and stage of aGvHD were determined according to the MAGIC criteria [24]. SR/SD status were evaluated according to consensus definitions developed by the EBMT-NIH-CIBMTR task force [25]. The best ORR was defined as the number of patients who obtained a complete (CR) or partial response (PR) at any time for the first exposure. Timely events were estimated with Kaplan-Meier/competing risk models with 95% confidence intervals (CIs). Treatment duration was defined as the time from the onset of treatment to the end of treatment or death (event), or EOS (censoring event). Time to best overall response and time to CR were defined as the time from the onset of treatment to the best overall response or CR (event), respectively, with ruxolitinib discontinuation, death, or EOS considered as censoring events. Loss of response was defined as the time from the best overall response to aGvHD progression (event), cGvHD or death due to a relapse of the underlying hematologic disease (competing events), or other non-GvHD deaths or EOS (censoring events). OS was defined as the time from the onset of treatment to death (event) or EOS (censoring). The association of characteristic and treatment response with OS was assessed with a Cox proportional hazards model with age as a continuous covariate, sex and Charlson comorbidity index [26] as categorical covariates, and the type of response (CR, PR, or no response) as a time varying covariate.

Public all-cause healthcare resource utilization (HCRU) was estimated using national register data on healthcare contacts. The corresponding costs were determined based on the unit costs of the healthcare in Finland 2017, scaled to 2022 prices using price index of public healthcare expenditure [27, 28]. The unit costs include the average cost of procedures, operations, laboratory examinations, inpatient medications, and overheads of contacts for each specialty field and contact type. The costs of ruxolitinib were also separately assessed using the dosing data and the retail prices as of May 2023 with value-added tax included. The HCRU and corresponding costs were assessed as per patient year estimates by diving the number of contacts/costs by the total number of patient years. 95% CIs were estimated using bootstrapping over the patients (10 000 samples).

Statistical analyses were performed using R, A Language and Environment for Statistical Computing, in R server environment, version 4.0.3 [29]. The significance level was 0.05.

Results

Patient characteristics

A total of 56 adult aGvHD patients treated with ruxolitinib from January 2019 through August 2021 were reviewed and characterized (Table 1). The median follow-up time from the first ruxolitinib exposure was 21.8 months (IQR:

Table 1 Patient characteristics

Variable	Overall ($N=56$)
Age at treatment initiation (years), median (IQR)	56.5 (41.2–63.4)
Length of follow-up (months), median (IQR)	21.8 (11.8–32.5)
Sex, n (%)	
Female	28 (50)
Male	28 (50)
Type of donor, n (%)	
Haploidentical relative	23-26[b]
HLA-identical sibling	< 5
Unrelated matched donor	29 (51.8)
Graft source, n (%)	
Bone marrow	< 5[b]
Peripheral blood	52-55[b]
Pretransplantation conditioning, n (%)	
MAC	28 (50)
RIC	28 (50)
GvHD prophylaxis, n (%)	
MTX-based	20 (35.7)
PTCy-based	36 (64.3)
First-line treatment, n (%)	
Corticosteroid	46 (82.1)
Other	10 (17.9)
Time from aGvHD diagnosis to ruxolitinib initiation (days), median (IQR)	10 (3–21)
aGvHD grade at treatment initiation, n (%)[a]	
Grade 1	15 (27.3)
Grade 2	23 (41.8)
Grade 3–4	17 (30.9)
Stage of skin at treatment initiation, n (%)[a]	
Stage 0	16 (29.1)
Stage 1	12 (21.8)
Stage 2	14 (25.5)
Stage 3–4	13 (23.6)
Stage of intestine at treatment initiation, n (%)[a]	
Stage 0	24 (44.4)
Stage 1	13 (24.1)
Stage 2	8 (14.8)
Stage 3–4	9 (16.7)
Stage of liver at treatment initiation, n (%)[a]	
Stage 0	55 (100)
Stage 2–4	0 (0)

[a] The proportion of patients for whom the respective data was available. A few patients had missing data on grade/stage (stage skin/liver, 1.8%; stage intestine, 3.6%)

[b] Due to the anonymity requirement of the data authority, results with low subject numbers were masked and it was ensured that the masked numbers cannot be deduced based on other available numbers

Abbreviations: aGvHD, acute graft-versus-host disease; HLA, human leukocyte antigen; IQR, interquartile range; MAC, myeloablative conditioning [high-dose cyclophosphamide (HDCy) + high-dose busulfan (HDBu), HDCy + total body irradiation 12 Gy (TBI12Gy), treosulfan 14 g/m^2/day + fludarabine (Flu), or other]; MTX-based, methotrexate-based [methotrexate + calcineurin inhibitor (CNI)/mammalian target of rapamycin (mTOR) ± anti-thymocyte globulins (ATG)/anti-T lymphocyte globulins (ATLG) ± corticosteroid (CS) ± mycophenolate mofetil (MMF)]; PTCy-based, post-transplant cyclophosphamide-based (HDCy + CNI/mTOR ± MMF); RIC, reduced-intensity conditioning [Flu + two-day busulfan ± thiotepa, FluCy ± TBI 2Gy, Flu + treosulfan 10 g/m^2/day]; SR/SD, steroid-refractory or -dependent

11.8–32.5). The patients were transplanted either at Turku or Helsinki University Hospitals, the two centers performing all allo-HSCTs for adults in Finland. Between 2019 and 2021, approximately 380 adult patients received an allo-HSCT in Finland, and 15% of them were treated with ruxolitinib for aGvHD.

Of the 56 ruxolitinib-treated aGvHD patients, 77% were transplanted for acute myeloid/monocytic ($n=17$) or lymphoblastic leukemia ($n=7$), or high-risk myelodysplastic syndrome ($n=19$). Nearly all patients received peripheral blood stem cell transplant, either from haploidentical relative or unrelated matched donor (Table 1). Myeloablative conditioning and reduced-intensity conditioning were equally used, and 64% ($n=36$) received post-transplant cyclophosphamide for GvHD prophylaxis (Table 1).

At the start of the ruxolitinib treatment, 42% of the patients manifested grade 2 aGvHD and 31% grade 3–4, while 27% of the patients had mild grade 1 aGvHD (Table 1). Ruxolitinib was also used in the front line for patients with high-risk and severe aGvHD. The median time from aGvHD diagnosis to the first ruxolitinib exposure was 10 days (IQR: 3–21).

Clinical outcomes of ruxolitinib-treated aGvHD patients

The best ORR at any time for the first ruxolitinib exposure was 91% (95% CI: 83.5–98.5; $n=51/56$; Fig. 1a). CR was achieved by 69.6% of patients ($n=39$) and PR by 21.4% ($n=12$). The median time to the best ORR was 28 days (95% CI: 21–38; Fig. 1b); the median time to CR was 30 days (95% CI: 22–45).

Of 39 patients with CR, 21 lost the response, while among 12 patients with PR, 7 experienced a loss of response during the follow-up. Time to loss of response was estimated with a competing risk model of aGvHD progression probability, where cGvHD and death due to a relapse of the underlying hematologic disease were considered as competing events (Fig. 1c). Acute GvHD progression rate was highest during the first three months reaching a plateau at approximately six months (Fig. 1c). At this time point,

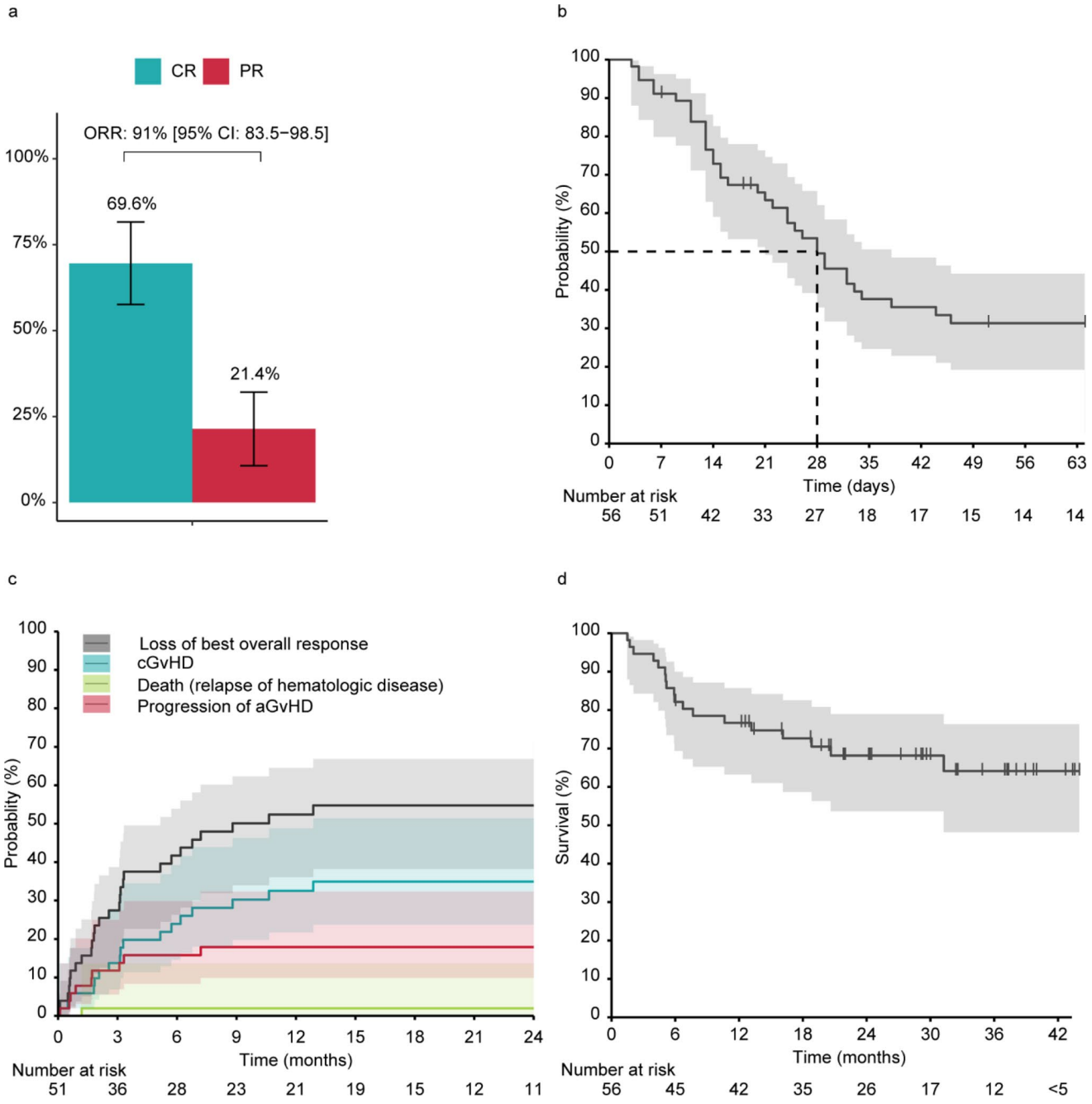

Fig. 1 **(a)** Best overall response rate (ORR; complete response, CR, or partial response, PR, obtained at any time for the first exposure); **(b)** time to best overall response; **(c)** aGvHD progression with the competing risks of cGvHD or death due to the relapse of the underlying hematologic disease; and **(d)** overall survival. 95% confidence intervals are included in the estimates

15.8% (95% CI: 8.4–29.8) of the patients were estimated to show aGvHD progression, 23.9% (95% CI: 14.6–39.2) had onset of cGvHD, and 2% (95% CI: 0.3–13.7) had died due to a relapse of the hematologic disease. Among those who obtained a response, the onset of cGvHD reached a plateau at approximately 12 months (32.5%; 95% CI: 21.7–48.7; Fig. 1c). Overall, the median time to loss of response due to aGvHD progression, cGvHD, or relapse-related death was 8.8 months (95% CI: 3.3–not reached; Fig. 1c). The median time to loss of response was 12.9 months (95% CI: 6.2–not reached) in patients with CR and 2.9 months (95% CI: 1.7–not reached) in patients with PR.

Of all ruxolitinib-treated aGvHD patients, 16% ($n=9/56$) had a relapse of the underlying hematologic disease during the follow-up and 32% died ($n=18/56$), with nine of GvHD (16%; $n=9/56$). Out of the patients who died of GvHD, five (56%) had obtained CR or PR. The nine patients who died of other reasons had all obtained CR or PR. The estimated three-year OS for all ruxolitinib-treated aGvHD patients was 64.1% (95% CI: 48.2–76.3; the median OS was not reached; Fig. 1d). The Cox regression model, adjusted for age, sex, and comorbidity burden, showed that patients who did not get CR or PR, had a 6.5-fold risk of death compared with patients with CR (hazard ratio: 6.47; 95% CI: 2.38–17.55; $p<0.001$).

Characteristics of ruxolitinib and corticosteroid treatments

Almost all patients received ruxolitinib as part of a combination therapy (Table 2). The median ruxolitinib daily dose was 10 mg both at the onset of treatment (IQR: 10–10) and one month later (IQR: 10–20). The median duration of the ruxolitinib treatment was 3.7 months (95% CI: 2.7–4.6;

Table 2 Characteristics of ruxolitinib and systemic corticosteroid treatments

Variable	Overall ($N=56$)
Type of ruxolitinib treatment, n (%)	
Any combination with ECP	21–24 (≈40)[c]
Any combination without ECP	31 (55.4)
Ruxolitinib monotherapy	<5[c]
Number of ECPs, median (IQR)	20.5 (12–23.5)
Ruxolitinib starting daily dose (mg), median (IQR)	10 (10–10)
Ruxolitinib daily dose after one month (mg), median (IQR)[a]	10 (10–20)
Duration of ruxolitinib treatment (months), median (95% CI)	3.7 (2.7–4.6)
Discontinuation of ruxolitinib, n (%)	
AE	8 (14.3)
Death	<5[c]
Good response (PR or better)	36 (64.3)
Lack of efficacy	<5[c]
Other	<5[c]
Relapse of underlying disease	<5[c]
Treatment ongoing at the end of follow-up	<5[c]
Received systemic CS during the follow-up, n (%)	51 (91.1)
On systemic CS at ruxolitinib discontinuation, n (%)[b]	
Yes	21 (41.2)
No	30 (58.8)
Daily dose of systemic CS at ruxolitinib discontinuation (mg/kg), median (IQR)[b]	0.1 (0.1–0.3)
Discontinued systemic CS during the follow-up, n (%)[b]	
Yes	34 (66.7)
No	17 (33.3)
Daily dose of systemic CS at the end of follow-up (mg/kg), median (IQR)[b]	0.2 (0.1–0.5)
SR/SD, n (%)	
Yes	35 (62.5)
No	8 (14.3)
Unknown	13 (23.2)

[a] Analyzed in patients who were on the treatment at one month

[b] Analyzed in patients who received systemic CS during the follow-up ($n=51$)

[c] Due to the anonymity requirement of the data authority, results with low subject numbers were masked and it was ensured that the masked numbers cannot be deduced based on other available numbers

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host disease; CI, confidence interval; CS, corticosteroid; ECP, extracorporeal photopheresis; IQR, interquartile range; PR, partial response; SR/SD, steroid-refractory or -dependent

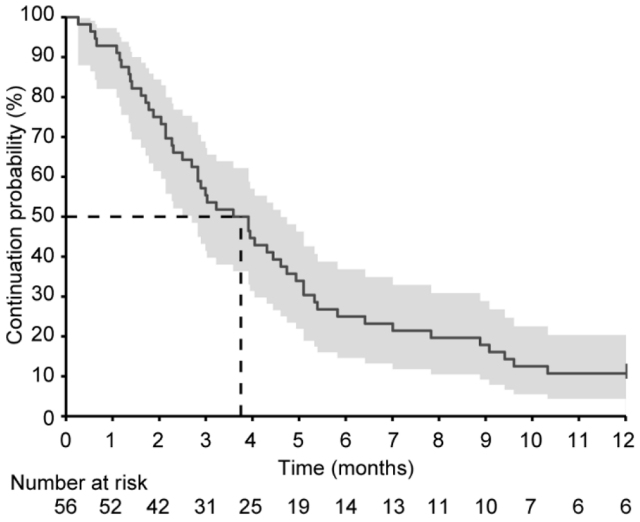

Fig. 2 Duration of ruxolitinib treatment with 95% confidence intervals

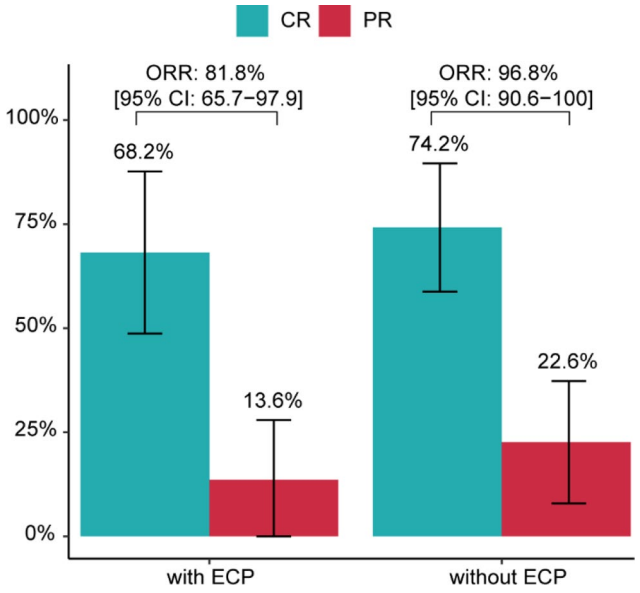

Fig. 3 Best overall response rate (ORR) at any time of patients treated with ruxolitinib combinations with or without extracorporeal photopheresis (ECP). CI, 95% confidence intervals; CR, complete response; PR, partial response

Fig. 2), and the most common cause of discontinuation was the achievement of good response (PR or better; 64%, $n=36$; Table 2).

Most patients (93%, $n=51$) were treated with systemic CSs: 82% ($n=46$) of the patients received CS as the first-line treatment of aGvHD. Two-thirds (63%; $n=35$) were considered as SR/SD (Table 2). Of the patients treated with systemic CSs, 67% ($n=34/51$) discontinued the treatment before the end of follow-up (EOF) and the remaining 33% ($n=17$) were on a median dose of 0.2 mg/kg (IQR: 0.1–0.5) at the EOF (Table 2).

Ruxolitinib and extracorporeal photopheresis (ECP)

Approximately 40% of the patients were treated with ECP (Table 2). The median number of treatment times per patient was 21. The best ORR remained statistically the same regardless of ECP use of the ruxolitinib-treated patients (Fig. 3).

Healthcare resource utilization (HCRU) in ruxolitinib-treated aGvHD patients

The total direct healthcare costs from the initiation of ruxolitinib treatment, and including e.g., the average costs of the inpatient medications, were 43 100€ per patient year. Of these costs, 23 700€ (95% CI: 16 700€–32 300€) were attributable to hospitalizations, 17 300€ (95% CI: 14 300€–20 600€) to outpatient specialty care contacts, 1 600€ (95% CI: 800€–2 800€) to primary care, and 500€ (95% CI: 400€–700€) to emergency care. Ruxolitinib costs, separately computed based on dosing data and median retail prices (with tax), were 7 400€ (95% CI: 5 500– 9 600€) per patient year.

Discussion

The present study provides real-world evidence on the use of ruxolitinib in the treatment of aGvHD. A total of 56 adult patients were characterized for their first ruxolitinib exposure. The proportion of ruxolitinib-treated aGvHD was approximately 15% among patients who underwent allo-HSCT in Finland 2019–2021. The ORR at any time was 91% and the best overall response was achieved within the median of one month. The median duration of ruxolitinib treatment was less than four months and the treatment was most often discontinued due to obtaining a good response, i.e., clinically meaningful PR or better (64%). The response was however estimated to be lost (either due to aGvHD progression, cGvHD, or hematologic relapse-related death) within the median of nine months. Two-thirds of the patients were able to discontinue CSs, and two-thirds were estimated to be alive at three years from the initiation of ruxolitinib treatment. Therefore, our study adds to the previous positive evidence on the efficacy and safety of ruxolitinib in the treatment of aGvHD [16, 30].

In a phase 3 randomized trial (REACH2) [16], the best ORR by day 28 was 82% (95% CI: 75–88; CR, 44%) and the day 28 ORR was 62% (95% CI: 54–70). In a phase 2 non-randomized, single-arm trial (REACH 1), the best ORR by day 28 was 55% (95% CI: 61–83; CR, 56%) and at any time, 73% (95% CI: 61–83) [30]. In the present study, the best ORR of 91% was based on the CR/PR obtained at any time, thus also including late responses. The differences in

the study setting and ORR definition may partly explain the higher probability of the loss of response observed in the real-world setting: 42% (95% CI: 26–54) of the patients lost the response at six months in the present study compared with 10% (95% CI: 4–17) in the REACH2 trial [16].

Thrombocytopenia, infection, and other adverse events as a reason of ruxolitinib discontinuation were recorded in only 14% of the patients, while the most common reason was obtaining a good response (64%). In the REACH 2 trial, the most common reason was a lack of efficacy (21%), while 11% of the discontinuations were due to adverse events [16, 31].

The long-term outcomes were also positive. Two-thirds of the patients were able to discontinue CSs before the EOF. In the REACH2 trial, use of CSs was assessed at day 56, where the discontinuation rate was 21% [16]. Moreover, the median OS was 11.1 months (95% CI: 0.60 − 1.15) in the clinical trial setting [16], while not reached in the present real-world study with the median follow-up time of 22 months.

This study benefited both from the structured data of the national registers and the high-quality local clinical data collected in the manual chart review. The management of GvHD is complex, and as this work was based on retrospective real-world data on a heterogenous patient population, causality between ruxolitinib treatment and long-term outcomes should be assessed with caution. The results of this non-interventional real-world study cannot be compared directly with those of the clinical trials due to differences in the outcome definitions and characteristics of the study population, which were not matched between the real-world and clinical trial settings [16, 30, 31]. Limitations also exist in the analysis of small patient subgroups. Moreover, the analysis of the HCRU did not contain a control group, and in the lack of specific diagnoses code for GvHD, included all-cause resource use.

There is a pressing need for efficient and safe therapies for aGvHD that can alleviate both disease of an individual patient and the burden on healthcare. In 2022, the European Medicines Agency approved the expanded use of ruxolitinib to patients with aGvHD [15]. Our study suggests that ruxolitinib appears effective and safe in real-world practice, thus complementing the outcome data from the clinical trials.

Data Availability

The single-level data cannot be shared. Only the original register holders or Finnish Social and Health Data Permit Authority can grant rights to third parties to use the data in accordance with the Act on Secondary Use of Health and Social Data.

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Author contributions M.I-R., H.M., K.U-R. and J.V. wrote the study protocol. E.M., A.K., H.R. and T.R. collected the data by chart-review. K.U-R. and J.V. wrote the manuscript and prepared figures/tables. J.V. conducted the statistical analyses. All authors reviewed the manuscript.

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Declarations

Human ethics and consent to participate Not applicable. This study was approved by the Finnish Social and Health Data Permit Authority, Findata, in accordance with the Act on Secondary Use of Health and Social Data.

Competing interests A.K., E.M., H.R. and T.R. have nothing to declare. H.M. is employed by Novartis Finland Oy. J.V. and K.U-R. are employed by Medaffcon Oy (Espoo, Finland), which received payments from Novartis for conducting the study. U.S. has been a member of advisory boards for Takeda, AstraZeneca, and Immedica, and provided consultancy to Viatris. M.I-R. has been a member of an advisory board for Novartis and provided consultancy to Incyte.

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