Topical ruxolitinib for chronic cutaneous graft-versus-host disease: a single-centre, randomised, double-blind, intra-patient-controlled phase 2 trial

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Summary

Background Oral ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, is approved for both acute and chronic graft-versus-host disease (cGVHD), whereas the topical formulation is approved for atopic dermatitis and vitiligo. Topical corticosteroids remain the mainstay for cutaneous cGVHD but their use is limited by adverse effects. We aimed to evaluate the clinical activity and safety of ruxolitinib 1·5% cream for epidermal or superficially sclerotic cutaneous cGVHD.

Methods In this single-centre, randomised, double-blind, intra-patient-controlled phase 2 trial at Memorial Sloan Kettering Cancer Center (NY, USA), patients aged 12 years or older with history of allogenic haematopoietic stem cell transplantation, with clinically confirmed, histologically confirmed, or both, cutaneous cGVHD involving at least 2% body surface area were randomly assigned to the body side receiving topical ruxolitinib 1·5% cream twice daily for 28 days; placebo vehicle was applied to contralateral lesional skin as a control. The primary endpoint was the absolute day-28 between-side difference in affected lesional body surface area (BSA), recorded as percentage of total BSA on each assigned side and analysed in evaluable patients; baseline between-side BSA differences were controlled for with adjusted mixed-effects regression. Only patients who completed the day 28 visit were included in the primary endpoint analysis; all patients who received any study treatment were included in the safety analysis. The trial is closed to enrolment and registered with ClinicalTrials.gov, NCT03954236. The trial is complete.

Findings Between June 28, 2019, and Sept 8, 2022, 24 patients were randomly assigned, with a median follow-up of 128 days (IQR 90–280). Median age was 47·5 years (IQR 32·5–67·5); 13 (54%) were female and 11 (46%) were male. At day 28, 23 patients were evaluable (one patient did not start treatment after screening visit due to intensive care unit admission). Mean affected lesional body surface area changed from 14·3% (SD 7·9) at baseline to 6·2% (6·7) with ruxolitinib and from 14·5% (8·0) to 10·4% (9·1) with placebo vehicle (difference –4·2 percentage points, 95% CI –6·8 to –1·5; p=0·0030); after adjustment for baseline between-side body surface are difference, the difference was –4·0 percentage points (–5·5 to –2·4; p<0·0010). Grade 3–5 treatment emergent adverse events were CNS leukaemia, sinusitis, and lung infection (one [4%] each); no treatment-related deaths occurred.

Interpretation Topical ruxolitinib showed significant clinical activity and favourable harms profile in active cutaneous cGVHD. Ruxolitinib cream could represent a steroid-sparing, skin-directed alternative or second-line therapy, expanding treatment options for patients with cutaneous cGVHD.

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Introduction

Chronic graft-versus-host disease (cGVHD), a prolonged immune-mediated disorder, is the leading cause of late non-relapse mortality after allogeneic haematopoietic stem cell transplantation,[1] negatively affecting quality of life and long-term outcomes.[2] The skin is the most commonly involved organ system.[1] A combination of pro-inflammatory cytokines, including interleukin-17 signalling, has been implicated in cutaneous cGVHD.[2–4]

Skin-directed therapies for cGVHD are scarce, with no approved US Food and Drug Administration (FDA) treatments. Topical corticosteroids are variably effective for localised cutaneous cGVHD or as an adjuvant therapy in patients with more advanced disease.[5] Topical corticosteroid use increases the risk of developing localised infections, striae, skin atrophy or thinning, bruising, acne, discoloration, and dependence; extensive use can cause systemic complications, such as hyperglycaemia and adrenal suppression.[6,7] Topical calcineurin inhibitors, including tacrolimus and pimecrolimus, are used with variable efficacy in body areas at greatest risk for topical corticosteroid adverse events, such as intertriginous areas and the face, and for incomplete response to or dependence on topical

Research in context

Evidence before this study

We searched PubMed/MEDLINE, Embase, Web of Science, ClinicalTrials.gov, and conference proceedings from Jan 1, 2000, to June 1, 2019, without language restrictions, using combinations of the terms "graft-versus-host disease", "GVHD", "chronic graft-versus-host disease", "cutaneous graft-versus-host disease", "skin graft-versus-host disease", "ruxolitinib", "Janus kinase inhibitor", "JAK inhibitor", "topical ruxolitinib", "topical JAK inhibitor", "cream", "lotion", "solution", and "topical". We also reviewed reference lists from relevant reviews and clinical guidelines. Existing evidence showed that topical corticosteroids and topical calcineurin inhibitors remained the principal skin-directed therapies for cutaneous chronic graft-versus-host disease (GVHD) despite little prospective evidence, variable efficacy, and substantial tolerability or long-term toxicity concerns. Oral ruxolitinib had shown emerging efficacy in steroid-refractory acute and chronic GVHD, although at the time of study initiation it was not yet approved for chronic GVHD (cGVHD). Topical Janus kinase (JAK) inhibitors, including ruxolitinib and tofacitinib, had shown clinical activity in immune-mediated dermatoses such as psoriasis, vitiligo, atopic dermatitis, and alopecia areata. In addition, topical kinase inhibition had shown activity in ocular GVHD, supporting the concept that localised inhibition of inflammatory signalling could have therapeutic relevance in GVHD. Preclinical murine skin GVHD studies provided particularly relevant rationale, showing that topical ruxolitinib reduced skin GVHD severity, decreased T-cell infiltration, preserved LGR5-positive hair follicle stem cells, and maintained skin homoeostasis in a manner distinct from topical corticosteroids. However, no prospective randomised clinical trials evaluating topical ruxolitinib for chronic cutaneous GVHD in humans were identified. The available evidence was limited by small studies, heterogeneous disease settings, absence of standardised cutaneous cGVHD response assessments, and absence of translational molecular analyses in human skin.

Added value of this study

This study provides the first randomised, double-blinded, intra-patient-controlled clinical trial evaluating topical ruxolitinib cream for cutaneous cGVHD. The findings extend existing evidence by showing clinically meaningful improvement in epidermal and superficially sclerotic cutaneous cGVHD with a favourable tolerability profile and without the cutaneous toxicities commonly associated with prolonged topical corticosteroid use. The study also provides novel translational data using non-invasive skin tape-strip transcriptomics, showing molecular changes associated with suppression of profibrotic and inflammatory signalling together with restoration of epithelial and immune homeostatic pathways in responders. These findings support the biological rationale for localised JAK1/2 inhibition in cutaneous cGVHD and identify potential molecular pathways associated with treatment response.

Implications of all the available evidence

Taken together with previous evidence supporting systemic JAK inhibition in cGVHD, these findings support topical ruxolitinib as a promising steroid-sparing skin-directed therapy for epidermal and superficially sclerotic cutaneous cGVHD. Topical JAK inhibition could provide an option for patients with localised body surface area involvement, incomplete response to conventional topical therapies, or those requiring reduction of topical corticosteroid exposure. These findings could inform future cGVHD management guidance and support broader access to topical ruxolitinib as an effective skin-directed treatment option. Use of topical ruxolitinib could help minimise cumulative topical corticosteroid exposure, reduce the need for systemic ruxolitinib in selected patients, and potentially delay or avoid escalation of systemic immunosuppressive therapies for predominantly cutaneous disease. The molecular findings also support further investigation of transcriptomic biomarkers and non-invasive skin sampling approaches to predict and monitor treatment response.

steroids.[8–12] However, a side-effect of burning sensation can limit their use.[13,14]

Janus kinases (JAKs) are intracellular non-receptor tyrosine kinases that contribute to T-cell activation, inflammation, and tissue damage.[15] An oral JAK 1/2 inhibitor, ruxolitinib, has shown efficacy for the systemic treatment of acute GVHD (aGVHD) and cGVHD and is FDA-approved for corticosteroid-refractory aGVHD and cGVHD.[16] However, adverse events are common, including cytopenia and infection risk, and limit its use.[16]

The topical formulation of ruxolitinib is approved by the FDA for the treatment of atopic dermatitis and non-segmental vitiligo,[17] and is being investigated for immune-mediated cutaneous diseases.[18–23] In dermatology studies, topical ruxolitinib has been associated with clinical activity and generally low systemic exposure, and in murine cutaneous GVHD models was associated with improved skin GVHD scores, reduced T-cell infiltration, and preservation of LGR5-positive hair follicle stem cells.[22–25] Given the activity of systemic JAK 1/2 inhibition in cGVHD and the need for steroid-sparing skin-directed therapies, we evaluated the clinical activity and safety–including short-term harms–of ruxolitinib 1·5% cream in patients with epidermal or superficially sclerotic cutaneous cGVHD.

Methods

Study design

This was a single-centre, double-blind, randomised, intra-patient-controlled, phase 2 trial at Memorial Sloan Kettering (MSK) Cancer Center (NY, USA), followed by

an open label extension for all patients who wished to continue. No patients or members of the public were involved in study design, conduct, or reporting. The trial adhered to the Declaration of Helsinki, local laws and regulations, and received ethics approval (18-412) from the MSK Institutional Review Board. The Data Safety and Monitoring Committee, which reports to the MSK Research Council and Institutional Review Board, provided trial monitoring. This study was registered with ClinicalTrials.gov, NCT03954236. The trial is complete.

Participants

Eligible patients were aged 12 years or older, with written informed consent obtained from all patients (including from a guardian for those <18 years), and at least 2% body surface area (BSA) involvement by clinically and/or histologically confirmed epidermal non-sclerotic chronic or superficially sclerotic cutaneous cGVHD after allogeneic haematopoietic cell transplantation according to the US National Institutes of Health (NIH) cGVHD consensus criteria. All lesional sites were eligible for treatment, and patients had to be able to apply topical interventions or have someone apply it for them. Previous topical therapies, including topical corticosteroids, calcineurin inhibitors, emollients, and phototherapy, were discontinued on day 0. Patients were required to have stable systemic GVHD treatment for at least 4 weeks before enrolment; planned systemic corticosteroid tapering was permitted. Modifications in systemic therapy for management of non-skin cGVHD were allowed during the trial (appendix p 2). Sex, race, and ethnicity were collected from medical records.

Exclusion criteria were a known history of allergy to any intervention ingredient, deep sclerotic cutaneous GVHD or cutaneous GVHD, use of concurrent topical therapy, changes in systemic therapy for skin GVHD during the trial, are considered a special population, concurrent participation in a similar trial or within a post-trial exclusion period, pregnancy or lactation, inadequate liver function (unless GVHD related), and active uncontrolled infection requiring systemic therapy (appendix pp 2–3).

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio for which side (left or right) of the face and/or body as applicable would receive topical ruxolitinib 1·5% cream; the contralateral side received placebo vehicle. The allocation sequence was generated using a random permuted block method without additional stratification variables and implemented through the MSK Clinical Research Database. Allocation was concealed from patients, investigators, treating clinicians, outcome assessors, and data analysts until completion of the day 28 (±3 days) visit. Only hospital pharmacists accessed treatment assignments to dispense masked study creams, which were labelled as left or right on the tube. Masking success was not formally evaluated.

Procedures

Patients were instructed to apply ruxolitinib 1·5% cream and placebo vehicle as a thin layer twice for 28 days to lesional areas on the assigned left or right side of the face and/or body as applicable. The placebo vehicle was the cream base used in the marketed product as supplied by the manufacturer and was not visually distinguishable from ruxolitinib cream. Investigators selected clinically comparable contralateral lesional areas where feasible. Patients had total body photography; these photographs will later be used to report the photograph-derived BSA. Lesional areas were outlined with surgical marker by a study investigator, and the patient was subsequently photographed again. The second set of photographs were provided to participants as an application reference along with written application instructions that specified a pre-designated number of fingertip units to be applied to the designated areas on each side, with equivalent BSA application on each side when possible and a maximum of 20% BSA per side during the randomised period. Marked treatment areas did not change if improvement or worsening was seen. If cutaneous findings resolved before day 28, patients were instructed to continue the assigned trial creams to day 28 unless toxicity or withdrawal criteria were met.

Follow-up continued to day 56 (±5 days). After completing the day 28 blinded period, patients were offered a 28-day open-label extension with application of ruxolitinib cream to both body sides to day 56. Patients who crossed over had additional safety follow-up at day 84 (±5 days). Criteria for participant removal from the trial included withdrawal of consent, unacceptable toxicity, investigator decision that continuation was not in the patient's best interest, or inability to complete required assessments. No dose reduction was planned for the topical cream; temporary interruption or discontinuation was permitted for suspected treatment-related toxicity.

See Online for appendix

Clinical assessments included BSA, Physician's Global Assessment (PGA) of Clinical Condition (appendix p 3), and Composite Assessment of Index Lesion Disease Severity (CAILS; appendix pp 3–4), all done at each visit (baseline and days 1, 14, 28, 56, and 84) by a masked trial dermatologist. BSA was assessed using a study-provided BSA calculator worksheet and was recorded separately for the ruxolitinib-treated and placebo vehicle-treated sides as the percentage of total BSA affected by active cGVHD lesions on each assigned side. Active disease was defined by erythema, scaling, papulosquamous or lichen planus-like change, or superficially sclerotic or lichen sclerosus-like change; post-inflammatory dyspigmentation alone was not counted as active BSA. PGA is used to evaluate overall improvement in cGVHD using a 0–6 scale where 0 is completely clear (100% improvement), 1–4 is almost clear to slight improvement, 5 is no change, and 6 is worse. Clinical response was assessed using a 6 point scale where 0 is complete

response, 1–3 is partial response, 4–5 is stable, and 6 is no response or progressive disease (appendix p 3). CAILS is a clinician-reported multidomain severity tool that separately scores erythema, scaling, and pruritus or itching as assessed during the provider visit using patient interview and examination findings such as excoriations and active scratching, and lesion size or BSA on each treated body side. An adapted skin-specific National Cancer Institute patient-reported outcomes (PRO)-CTCAE questionnaire assessing rash, dry skin, itch, sun sensitivity, and pain on each side of the body was also collected at protocol-specified visits.[26]

Total RNA sequencing was done on skin samples collected non-invasively by tape stripping using Smart Sticker (DermTech [San Diego, CA, USA]), which collects molecular information from epidermal cells, including corneocytes, keratinocytes, resident immune cells, and melanocytes. Samples were obtained from lesional skin at day 28, allowing transcriptomic comparisons between affected skin in the ruxolitinib and placebo vehicle groups and between clinical responders and non-responders.

Adverse events were evaluated from first treatment administration to trial completion or loss to follow-up. All adverse events were evaluated from first treatment administration to trial completion or loss to follow-up. Per protocol, only adverse events of grade 2 or higher were monitored and reported to day 56 (±3 days). Patients in the open-label extension were monitored and assessed up to day 84 (±5 days). Adverse events were tabulated by system organ class and grade according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Harms were assessed systematically at scheduled visits and with interval patient reports. Routine laboratory monitoring specifically for topical study treatment was not required by protocol; laboratory testing obtained as part of standard post-transplantation care was reviewed when decided by the site investigator as clinically relevant.

Outcomes

The primary endpoint was the absolute day-28 difference in affected lesional BSA between the ruxolitinib-treated and placebo vehicle-treated body sides. The measurement variable was active cutaneous cGVHD involvement; the analysis metric was percentage of total BSA affected on each assigned side. Secondary endpoints were PGA at day 28; CAILS at day 28; BSA, PGA, and CAILS at day 14; PROs at days 14 and 28; safety and tolerability; accrual, retention, and treatment adherence; and exploratory tape-strip RNA-sequencing profiles of lesional skin in the ruxolitinib versus placebo vehicle groups. Agreement between dermatologist-assessed and photograph-derived BSA was a prespecified ancillary methodological secondary endpoint; photograph-derived measurements were not used in the clinical activity analyses. Because this endpoint requires a separate imaging-validation and concordance analysis, it will be reported in a dedicated imaging manuscript.

Statistical analysis

For the primary clinical activity endpoint, affected lesional BSA was expressed as the percentage of total BSA affected on each assigned treatment side. The sample-size calculation assumed a total BSA of 1·8 m², equivalent to 18 000 cm². The originally specified detectable between-side difference of 327·1 cm² therefore corresponded to an absolute difference of approximately 1·82 percentage points of total BSA, and the assumed SD of 500 cm² corresponded to approximately 2·78 percentage points. Assuming a within-patient correlation of 0·40, a two-sided paired t test with an alpha level of 0·05 would provide 80% power to detect this difference in a target sample size of 24 patients (12 in each group).

Only patients who completed the day 28 visit were included in the primary endpoint analysis; all patients who received any study treatment were included in the safety analysis. Descriptive statistics and graphical methods summarised patient characteristics and the distribution of BSA, PGA, and CAILS at each evaluation time point. Paired t tests assessed between-side differences in BSA, PGA, and CAILS. The primary endpoint comparison was the absolute day-28 between-side difference in affected lesional BSA based on the paired t test. Expressing the endpoint in percentage points rather than cm² represents a linear rescaling and does not change the standardised effect size or statistical power. Associated figures of BSA, CAILS, and PGA response by treatment group are in the appendix (pp 4–7).

To control for baseline differences, mixed-effects regression was used with BSA difference as the outcome, time point as a categorical variable, and baseline difference between treatment sides included to control for imbalance. Unadjusted and adjusted estimates are presented with 95% CIs.

Secondary clinical activity endpoints were analysed according to outcome type. Continuous paired outcomes, including BSA, PGA, and CAILS at days 14 and 28, were compared between treatment sides using paired t tests. Clinical response categories were summarised descriptively using frequencies and percentages. PRO-CTCAE were summarised descriptively, and between-side comparisons at each study visit were performed using paired analyses appropriate for the outcome scale. Treatment adherence, accrual, retention, and safety outcomes were summarised descriptively. Treatment-emergent adverse events were tabulated by maximum CTCAE grade and system organ class. Exploratory analyses of tape-strip RNA sequencing were hypothesis-generating. Differential gene expression analyses were done between ruxolitinib-treated and placebo vehicle-treated samples and between clinical responders and non-responders, followed by pathway enrichment analyses. Because of the exploratory nature

of these analyses, no adjustment for multiple comparisons was applied. Post-hoc analyses included descriptive evaluation of clinical response among patients with previous or concurrent systemic ruxolitinib exposure. These analyses were considered exploratory and were not adjusted for multiple testing. Unadjusted and adjusted estimates are presented with 95% CIs. All analyses were performed using StataMP version 16 (StataCorp, College Station, TX, USA).

Protocol deviations were reviewed through MSK Institutional Review Board (IRB)/Privacy Board reporting procedures. The regulatory files provided for revision included 10 prospective IRB-approved deviation requests and 50 retrospective deviation reports. The prospective deviations comprised home shipment of study drug (n=1), at-home tape-strip collection by one participant after a cancelled in-person visit (n=1), and extensions of open-label ruxolitinib cream beyond the protocol-defined treatment period for participants with perceived clinical benefit (n=8). Retrospective deviations were unanticipated, primarily administrative or conduct-related, including out-of-window or missed visits or assessments, incomplete or unsigned treatment diaries, PRO-CTCAE questionnaires, or drug-accountability records, missed doses, and informed-consent documentation deficiencies. All deviations were accompanied by corrective action plans without affecting treatment assignment, masking, safety interpretation, or the day-28 primary endpoint analysis. IRB-approved protocol amendments incorporated procedures for study-drug shipment and optional treatment-extension follow-up. All protocol amendments were approved before implementation.

Role of the funding source

This trial was funded by Incyte through investigator-initiated research funding, and Incyte provided the trial treatments. MSK was the study sponsor. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 15, 2019, and Sept 8, 2022, 531 patients were assessed for eligibility; 507 were excluded because they did not meet inclusion criteria (appendix p 2). Screening was driven by a broad database search identifying any mention of GVHD in patient records, but many records reflected previous GVHD rather than active disease, acute rather than chronic GVHD, non-skin GVHD, or patients who did not meet study requirements. No patients declined participation, and no exclusions were due to other reasons (figure 1). 24 patients were randomly assigned between June 28, 2019, and Sept 8, 2022. Median age was 47·5 years (IQR 32·5–67·5); 13 (54%) of 24 patients were female and 11 (46%) were male. 14 (58%) of 24 participants reported their race as White, four (17%) Asian, three (13%) Black, one (4%) American Indian or Native American, and two (8%) as other; five participants (21%) reported Hispanic ethnicity. The underlying haematological diagnoses in the 24 participants were acute leukaemias (16 [67%]), non-Hodgkin lymphomas (four [17%]), and other diagnoses (four [17%]; table 1). The median time from allogeneic haematopoietic cell transplantation to enrolment was 455 days (IQR 357–1020), and from cGVHD onset to enrolment was 132 days (IQR 19–385). Median follow-up for the analyses presented was 128 days (IQR 90–280). At trial initiation, global NIH cGVHD severity, encompassing all involved organs, was mild in two (8%) of 24 patients, moderate in 19 (79%), and severe in three (13%). NIH skin organ severity was mild in four (17%) of 24, moderate in 19 (79%), and severe in one (4%). This NIH skin score reflects the standard organ severity scoring framework and is not equivalent to the percentage of total BSA selected for trial cream application;[27] therefore, patients could have moderate skin organ severity while having little bilateral target-lesion BSA suitable for topical treatment. Most patients (21 [88%] of 24) had epidermal cGVHD, including lichen planus-like (11 [46%]), papulosquamous (seven [29%]), and maculopapular rash or erythema (three [13%]) features. The remaining three patients had superficial lichen sclerosus-like cGVHD; no patients with deeper sclerosis, fasciitis, or joint or fascial restriction

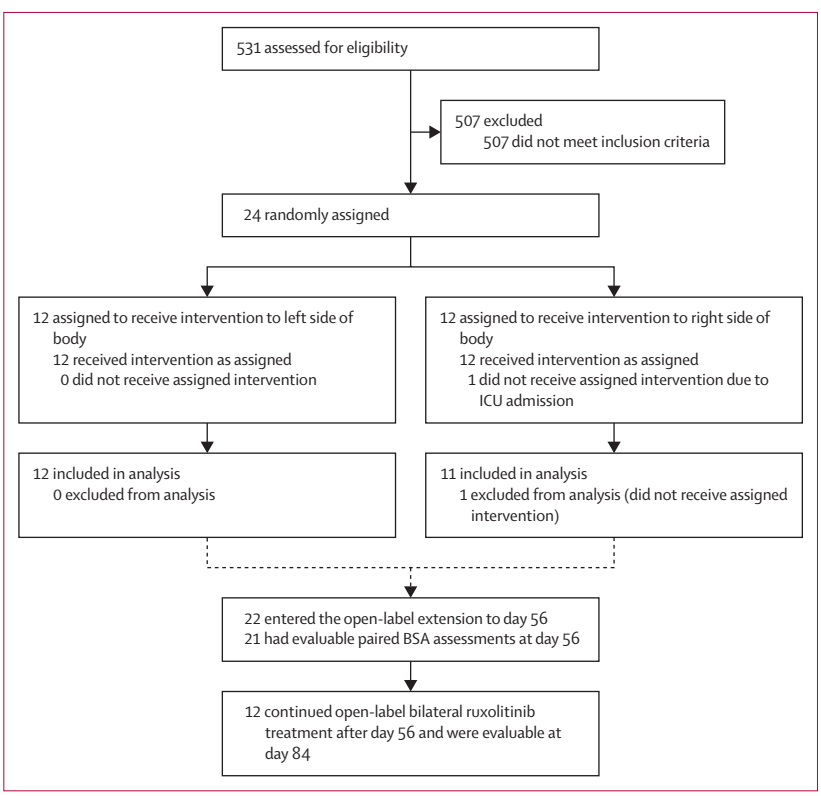

Figure 1: **Trial profile**
BSA=body surface area. ICU=intensive care unit.

requiring systemic sclerosis-directed therapy were recruited.

Patients had received a median of two (IQR 1–2; range 0 to 11) previous systemic treatments for cGVHD, and most continued concurrent systemic treatment during the trial. Between days 0 and 28, two patients initiated prednisone for non-cutaneous cGVHD, and prednisone was tapered in two patients. No new systemic GVHD therapies were introduced between days 28 and 56. During this interval, prednisone dose was increased in one patient for a non-cutaneous cGVHD indication and was tapered in another patient. Most patients had also, before recruitment, not responded to at least two topical

	Patients (N=24)
Median age, years (IQR)	47·5 (32·5–67·5)
Female sex	13 (54%)
Male sex	11 (46%)
Race	
White	14 (58%)
Asian	4 (17%)
Black	3 (13%)
American Indian/Native American	1 (4%)
Other	2 (83%)
Ethnicity	
Hispanic	5 (21%)
Non-Hispanic	19 (79%)
Diagnosis	
Acute lymphoblastic leukaemia	6 (25%)
Acute myeloid leukaemia	10 (42%)
Chronic myeloid leukaemia	1 (4%)
Non-Hodgkin lymphoma	4 (17%)
Myelodysplastic syndrome or myeloproliferative disorder	2 (8%)
Aplastic anaemia	1 (4%)
Hematopoietic stem cell transplantation conditioning	
Myeloablative	9 (38%)
Non-myeloablative	2 (8%)
Reduced intensity	13 (54%)
Donor	
Matched related donor	7 (29%)
Mismatched unrelated donor or haploidentical	7 (29%)
Matched unrelated donor	10 (42%)
8/8 allele-matched unrelated donor	1 (4%)
7/8 allele-matched unrelated donor	1 (4%)
<7/8 allele-matched unrelated donor	8 (33%)
Stem cell source	
Bone marrow	1 (4%)
Cord blood	6 (25%)
Peripheral blood stem cells	17 (71%)
Graft-versus-host disease prophylaxis	
CNI or methotrexate with or without mTORi	12 (50%)
CNI or mycophenolate mofetil	4 (17%)
CNI or mycophenolate mofetil plus post-transplantation cyclophosphamide	1 (4%)
Ex vivo CD34+ selected T-cell depletion with or without CNI	7 (29%)

Data are n (%) unless otherwise stated. CNI=calcineurin inhibitor. mTORi=mammalian target of rapamycin inhibitor.

Table 1: **Baseline patient characteristics**

	Patients (N=24)
Median time from chronic GVHD onset to enrolment, days (IQR)	132 (19–385)
Chronic graft-versus-host disease subtype	
Classic	14 (58%)
Overlap	10 (42%)
Extracutaneous involvement of chronic GVHD	
Oral	9 (38%)
Ocular	8 (33%)
Gastrointestinal	7 (29%)
Pulmonary	4 (17%)
Liver	3 (12%)
Muscular	3 (12%)
Joint	2 (8%)
Genitourinary	2 (8%)
Previous lines of systemic therapy	
0	4 (16%)
1	5 (21%)
2	10 (42%)
≥3	5 (21%)
Previous systemic therapies for GVHD	
Systemic steroids	12 (50%)
Ruxolitinib	4 (17%)
Sirolimus	3 (13%)
Belumosudil	2 (8%)
Tocilizumab	1 (4%)
Ibrutinib	1 (4%)
Rituximab	1 (4%)
Extracorporeal photopheresis	3 (13%)
Concurrent systemic therapies for GVHD	
Systemic steroids	7 (29%)
Ruxolitinib	3 (13%)
Sirolimus	2 (8%)
Belumosudil	2 (8%)
Tocilizumab	1 (4%)
Cutaneous chronic GVHD type	
Epidermal	21 (87%)
Lichen planus-like	11 (45%)
Papulosquamous	7 (29%)
Maculopapular rash or erythema	3 (13%)
Superficially sclerotic	3 (13%)
Lichen sclerosus-like	3 (13%)
Previous topical lines of therapy	
Topical corticosteroids	21 (88%)
Topical calcineurin inhibitors	10 (42%)
Phototherapy	7 (29%)

Data are n (%) unless otherwise stated. N=24. GVHD=graft-versus-host disease.

Table 2: **Baseline graft-versus-host disease characteristics**

therapies, including topical corticosteroids (21 [88%] of 24 patients), topical tacrolimus (ten [42%]), and phototherapy (seven [29%]; table 2).

The primary endpoint was assessed in 23 patients at day 28; one patient did not start treatment after the screening visit due to intensive care unit admission. At baseline, mean affected lesional BSA was similar on the ruxolitinib and placebo vehicle sides (14·3% [SD 7·9] *vs* 14·5% [SD 8·0] of total BSA on each assigned side; table 3; appendix p 4). By day 28, mean affected lesional BSA decreased to 6·2% (SD 6·7) on the ruxolitinib-treated side and 10·4% (SD 9·1) on the placebo vehicle-treated side (difference –4·2 percentage points, 95% CI –6·8 to –1·5; p=0·0030), corresponding to relative reductions from baseline of 56·6% and 28·3%, respectively (figure 2). After adjustment for baseline between-side BSA difference, the between-side difference was –4·0 percentage points (–5·5 to –2·4; p<0·0010).

At day 14, 22 (92%) of 24 patients were evaluable. Mean affected lesional BSA was lower with ruxolitinib than with placebo vehicle (7·7% *vs* 10·4%; p=0·0020). Clinical response, according to PGA of Clinical Condition, on the ruxolitinib-treated side at day 28 occurred in 17 (74%) of 23 evaluable patients: five (22%) had complete response and 12 (52%) had partial response. The remaining six (26%) of 23 had no response or stable cutaneous lesions. The six non-responders included five patients with epidermal cGVHD, of whom four had lichen planus-like features and one had maculopapular rash or erythema, and one patient with superficial lichen sclerosus-like cGVHD. Non-responders had NIH skin scores of 1 (three patients), 2 (two patients), and 3 (one patient). Before enrolment, non-responders had also not responded to systemic corticosteroids (four patients) and tocilizumab (one patient), as well as topical corticosteroids (five patients), topical tacrolimus (three patients), narrowband ultraviolet B phototherapy (one patient), or ultraviolet A phototherapy (one patient). PGA scores on day 1 of the trial were similar, with mean scores of 5 points on both the ruxolitinib and placebo vehicle sides (SD 0 for both sides, table 3; appendix pp 5–6). By day 14, mean PGA scores were 2·7 (SD 1·8) on the ruxolitinib side versus 3·8 (SD 1·7) on the placebo vehicle side (p=0·0020), and at day 28, 1·9 (SD 1·5) versus 3·7 (SD 1·6; p=0·0004). CAILS scores were similar at baseline: mean 15·0 (SD 5·7) for ruxolitinib versus 15·3 (SD 5·5) for placebo vehicle (p=0·12; table 3; appendix p 7). By day 14, mean CAILS scores were 6·9 (SD 5·1) with ruxolitinib versus 11·0 (SD 6·7) with placebo vehicle (p=0·0009), and at day 28 were 5·8 (SD 4·9) versus 10·6 (SD 6·8; p=0·0040).

Side-specific adapted PRO-CTCAE results did not show significant between-side differences, but did show that symptom burden was generally low and improved or remained stable over time on both treatment sides (appendix pp 13–15). Rash prevalence fell from 18 (75%) of 24 patients at screening to eight (35%) of 23 patients at day 28 on both the ruxolitinib-treated and vehicle-treated sides, with no significant between-side differences at any time point. Dry-skin severity decreased from 1·9 at screening to 1·1 by day 14 and remained about 1·1 at day 28 on both treatment sides. Itch severity also decreased over time, from 1·0–1·2 at screening to 0·7 on the ruxolitinib-treated

	Screening (baseline)	Day 1 before treatment	Day 14	Day 28	Day 56*	Day 84*
Percentage of total body surface area affected on assigned side						
Ruxolitinib side, mean (SD)	14·3% (7·9)	14·4% (7·9)	7·7% (7·1)	6·2% (6·7)	3·8% (4·3)	4·5% (9·9)
Placebo vehicle side, mean (SD)	14·5% (8·0)	14·5% (8·0)	10·4% (7·8)	10·4% (9·1)	3·8% (4·2)	4·3% (9·5)
n	24	24	22	23	21	12
p value	0·10	0·10	0·0020	0·0030	0·49	0·36
Physician's Global Assessment score						
Ruxolitinib side, mean (SD)	..	5 (0)	2·7 (1·8)	1·9 (1·5)	1·4 (1·6)	1·5 (1·8)
Placebo vehicle side, mean (SD)	..	5 (0)	3·8 (1·7)	3·7 (1·6)	1·5 (1·6)	1·5 (1·9)
n	..	24	22	23	21	12
p value	..	..	0·0020	0·0004	0·16	0·71
Composite Assessment of Index Lesion Severity score						
Ruxolitinib side, mean (SD)	15·0 (5·7)	15·3 (5·5)	6·9 (5·1)	5·8 (4·9)	4·2 (4·3)	4·2 (5·0)
Placebo vehicle side, mean (SD)	15·3 (5·5)	15·7 (5·3)	11·0 (6·7)	10·6 (6·8)	4·8 (4·2)	4·3 (5·2)
n	24	24	22	23	21	12
p value	0·12	0·23	0·0009	0·0040	0·080	0·82

*Day 56 and day 84 denominators denote paired evaluable assessments (day 56, n=21; day 84, n=12).

Table 3: **Clinical activity endpoints**

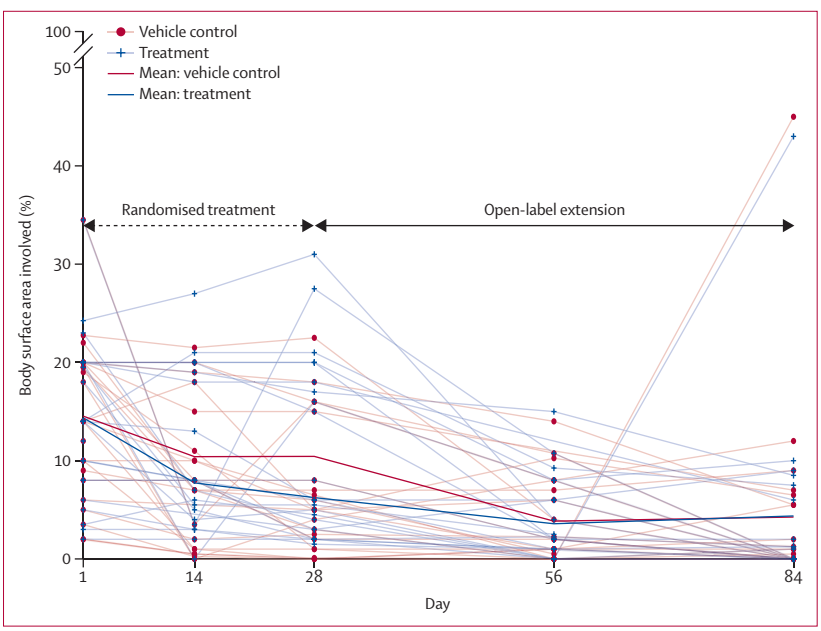

Figure 2: **Body surface area involvement by initial study group**

side and 0·6 on the placebo vehicle-treated side at day 28, again without significant between-side differences. Sun sensitivity and pain scores were infrequent and low, and no significant side-specific differences were observed to day 84. Patients reported high treatment adherence, with a median of two missed doses (range 0–12) during the first 28 days of treatment. Treatment diaries were available for 21 patients: 16 completed diaries in full, one had 1 week of missing data, and four had 2 weeks of missing data.

22 patients entered the open-label extension to day 56; 21 had evaluable paired BSA assessments at day 56. 12 patients continued open-label bilateral ruxolitinib treatment after day 56 and were evaluable at day 84. In patients who crossed over or continued ruxolitinib to day 56, mean lesional BSA was 3·8% on both the original treatment (SD 4·3) and original placebo vehicle sides (SD 4·2; p=0·49). In the 12 patients evaluable at day 84, mean lesional involvement was 4·5% (SD 9·9) and 4·3% (SD 9·5) on the originally assigned treatment and placebo vehicle sides, respectively (p=0·36). During the open-label extension phase, PGA scores were similar between the originally assigned sides at day 56 (1·4 [SD 1·6] ruxolitinib *vs* 1·5 [SD 1·6] placebo vehicle; p=0·16) and day 84 (1·5 [SD 1·8] *vs* 1·5 [SD 1·9]; p=0·71). CAILS scores were not significantly different between originally assigned sides at day 56 (4·2 [SD 4·3] ruxolitinib *vs* 4·8 [SD 4·2] placebo vehicle; p=0·080) or day 84 (4·2 [SD 5·0] *vs* 4·3 [SD 5·2]; p=0·82).

Four (17%) of 24 patients had five treatment-emergent adverse events of grade 2 or higher, including two serious adverse events (table 4). Events were deemed unrelated or unlikely to be related to trial therapy, and included cuticle fissures (two grade 2 events), sinusitis (one grade 3 event), lung infection (one grade 3 event), and leukaemia progression (one grade 5 event) six months after trial treatment. No treatment-related deaths occurred, and no treatment interruptions or dose modifications were required because of toxicity.

Total RNA-sequencing was done on skin samples collected at day 28 non-invasively by tape stripping of both body sides, allowing comparisons between affected skin in the ruxolitinib and placebo vehicle groups and between clinical responders (17 patients) and non-responders (five patients). A total of 2170 differentially expressed genes were identified between the ruxolitinib and vehicle groups (fold change >2; p<0·050), with 623 differentially expressed genes distinguishing responders and non-responders (fold change >2; p<0·050; appendix pp 7–13). Pathway enrichment analyses were exploratory. The most significantly altered pathways between ruxolitinib-treated and placebo vehicle-treated samples included neuroactive ligand-receptor interaction, PD-1 signalling, and expression and translocation of olfactory receptors (appendix pp 7–13). Pathways differing between responders and non-responders included *Staphylococcus aureus* infection, NOD-like receptor signalling, IL-17 signalling, NF-κ-B signalling, and Th17 cell differentiation (appendix pp 7–13).

Four patients had previous exposure to or were considered refractory to oral ruxolitinib before study enrolment, and three patients were receiving systemic ruxolitinib during the trial. On post-hoc analysis, clinical response on the ruxolitinib-treated side occurred in all seven of these patients. Exploratory transcriptomic comparisons by systemic ruxolitinib exposure were not considered interpretable because the subgroup was too small for meaningful omics comparison.

	Grade 2	Grade 3	Grade 4	Grade 5 (deaths)
Cuticle fissures	2 (8%)	0	0	0
Sinusitis	0	1 (4%)	0	0
Lung infection	0	1 (4%)	0	0
CNS leukaemia progression	0	0	0	1 (4%)

Data are n (%). N=24.

Table 4: **Treatment-emergent adverse events of grade 2 or higher**

Discussion

In this double-blind, randomised, intra-patient-controlled, phase 2 trial, topical ruxolitinib 1·5% cream reduced active lesional BSA more than placebo vehicle by day 28 in patients with epidermal or superficially sclerotic cutaneous cGVHD. The paired design allowed direct comparison of active drug and placebo vehicle within the same individual, reducing confounding from heterogeneous transplantation history, systemic GVHD therapy, and baseline cGVHD phenotype. Improvement was detectable by day 14 and was accompanied by improvements in clinician-assessed PGA and CAILS scores.

The placebo vehicle-treated body side also improved, which is important for interpretation. Improvement on the placebo vehicle side was plausible because patients remained on background systemic therapy with some corticosteroid tapering or escalation for non-cutaneous indications, and vehicle or emollient effects; nevertheless, the greater reduction on the ruxolitinib side supports a treatment-specific effect. The intra-patient design was chosen to address these issues. The greater reduction on the ruxolitinib-treated side at the day 28 primary endpoint supports a treatment-specific effect.

PGA and CAILS improved along with the primary BSA endpoint,[28,29] supporting the internal consistency of the clinical findings. Side-specific adapted PRO-CTCAE was collected, but no significant between-side differences were observed and several participants reported difficulty separating symptoms by body side (appendix pp 13–15); this is a limitation, because symptoms such as itch, pain, tightness, sleep disruption, and treatment burden are central to patient experience in cutaneous cGVHD. Future trials should include validated patient-reported outcomes designed for side-specific or lesion-specific symptom attribution.

Topical ruxolitinib was associated with little short-term toxicity in this small study. No patient required treatment interruption or dose modification because of toxicity, and no treatment-related deaths occurred. Unlike topical corticosteroids, no cases of skin atrophy, thinning, or increased bruising were reported, underscoring the favourable safety profile and localised cutaneous effect of topical ruxolitinib. Longer-term risks of topical ruxolitinib in this immunocompromised population, including infection and secondary malignancy risk, require additional follow-up.

Tape-strip RNA sequencing identified molecular changes consistent with attenuation of JAK-dependent immune signalling and restoration of epidermal barrier homoeostasis in ruxolitinib-treated lesions. Differences between responders and non-responders suggested broader reprogramming of immune, repair, and profibrotic pathways. Because ruxolitinib does not directly inhibit IL-17, enrichment of IL-17–related signalling in responders might reflect redistribution toward barrier-protective immunity after suppression of dominant inflammatory circuits rather than persistent pathogenic activity.[30,31] These exploratory findings require prospective validation before any pathway can be considered predictive of response, and they also support tape stripping as a feasible non-invasive pharmacodynamic approach in cutaneous cGVHD, consistent with the SCRATCH-AD study,[19] in which topical ruxolitinib modulated tape-strip biomarkers in atopic dermatitis.

Systemic absorption is possible with topical ruxolitinib, but previous dermatology studies have reported generally low plasma concentrations after twice-daily application. These data provide safety context for topical use; however, plasma ruxolitinib concentrations were not measured in the our trial, and cytopenias were not systematically monitored as a topical ruxolitinib-specific endpoint because concurrent systemic therapies would have confounded interpretation.

Several limitations should be considered. This was a single-centre study with a small sample size, short blinded treatment period, and no enrolled paediatric patients. Only three patients had superficial lichen sclerosus-like disease, limiting conclusions about sclerotic manifestations. Although all four patients with previous systemic ruxolitinib exposure or refractoriness and all three patients receiving concurrent systemic ruxolitinib responded clinically, the study was not designed to establish whether previous refractoriness to systemic ruxolitinib predicts topical response, and the subgroup was too small for definitive clinical or transcriptomic inference. In addition, patients with deeper sclerosis, fasciitis, or diffuse extensive cutaneous involvement were not represented.

In summary, topical ruxolitinib 1·5% cream improved active lesional BSA over 28 days compared with placebo vehicle in selected patients with epidermal or superficially sclerotic cutaneous cGVHD and had little short-term toxicity. The results of this trial underscore the therapeutic potential of skin-directed therapy with ruxolitinib cream in cutaneous cGVHD. Clinical improvement was observed within weeks, with minimal associated toxicity, supporting the use of this topical therapy as a valuable adjuvant to systemic therapy or as sole intervention in cases without extensive BSA involvement.

Contributors

AM and SD accessed and verified all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AM was responsible for study concept and design, with design support from DMP, M-AP, and MEL. AM, DMP, AH, and MEL were responsible for acquisition, analysis, or interpretation of data. AM, JO, VR, IN, SD, TM, MEL, BCS, M-AP, AH, and DMP drafted the manuscript. VR, EBP, RA, RT, BCS, MS, and AH critically reviewed the manuscript for important intellectual content. SD, RA, JO, and JK conducted the statistical analysis. AM obtained funding and provided supervision. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

De-identified individual participant data underlying the results reported in this article (including data dictionaries) will be made available beginning 3 months and ending 5 years following article publication to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to the corresponding author via email. To gain access, data requestors will need to sign a data access agreement. Data will be shared for individual participant data meta-analysis and for other methodologically sound proposals.

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