



A Prebiotic and Panthenol-Containing Repair Balm Improves Tolerability of Topical 5-Fluorouracil Field Therapy for Actinic Keratoses: A Randomised Controlled Trial

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ABSTRACT

Introduction: Topical 5-fluorouracil (5-FU) is an effective field therapy for actinic keratoses (AKs) with proven chemopreventive benefit; however, treatment-limiting local skin reactions frequently impair tolerability and adherence in clinical practice. Our objective is to determine whether adjunctive use of a prebiotic and panthenol-containing repair balm (BB5+ repair balm) improves tolerability and treatment adherence to topical 5-FU field therapy for AKs compared with standard of care alone.

Methods: We conducted a single-blind, randomised controlled trial involving adults prescribed topical 5-FU for AKs on the face/scalp or

hands/forearms. Participants were randomised 1:1 to standard of care (5-FU twice daily) or intervention (5-FU twice daily plus BB5+ repair balm applied 30 min after 5-FU), stratified by treatment site and immunocompetence. Primary outcomes were treatment adherence (≥ 42 applications over four weeks) and worst local skin reaction (LSR) score using a validated severity scale. Secondary outcomes included LSR scores at weeks 1–4 and Dermatology Life Quality Index (DLQI).

Results: In all, 59 participants consented, and 50 completed the study (27 intervention, 23 control). Completion of ≥ 42 applications occurred in 59% of the intervention group and 52% of controls (non-significant). Mean total applications were similar between groups (39.6 versus 39.9). The intervention group demonstrated lower mean worst LSR scores compared with standard care (9.2 versus 10.2) with significantly reduced severity at day 14 ($p=0.0435$) and day 21 ($p=0.0054$), particularly for face/scalp treatments. DLQI scores were significantly improved in facial treatment subgroups receiving BB5+ repair balm.

Conclusions: Although adjunctive BB5+ repair balm did not increase overall treatment completion, it significantly reduced local skin reaction severity and improved quality of life, particularly for facial field therapy. Adjunctive barrier repair may enhance tolerability of topical 5-FU

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and support patient experience during actinic keratosis treatment.

Trial Registration: The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12624000911594).

PLAIN LANGUAGE SUMMARY

Chronic sun exposure is responsible for the majority of skin cancers, and in this process it generates actinic keratoses, commonly called sun spots, that are a form of precancerous reaction of the skin. Treatment of the sun-exposed skin and actinic keratoses with 5-fluorouracil (5-FU) has been reported as the most effective way to prevent the onset of new skin cancers. However, topical 5-FU is not well tolerated and has many side effects, limiting its acceptability by patients. The aim of this study was to see whether using a prebiotic and panthenol repair dermocosmetic balm alongside topical 5-fluorouracil (5-FU) could reduce skin toxicity and improve patients' ability to complete treatment. We performed a randomised controlled trial where we looked at adults who were prescribed topical 5-FU for actinic keratoses on the face, scalp, arms or hands. Participants were randomly assigned to receive standard treatment with 5-FU alone or 5-FU plus an additional repair balm Baume B5+ (named BB5+), applied 30 min later. The treatment duration was 4 weeks, where skin reactions, treatment completion rates and quality of life were assessed. Patients using the barrier repair cream experienced less severe skin irritation, and reported better quality of life during treatment. The total amount of treatment completed was similar in both groups. Using a barrier repair cream alongside topical 5-FU may help reduce skin toxicities and improve comfort during treatment, especially for the face. This simple approach may improve patients' experience of treatment in routine clinical practice.

Keywords: Fluorouracil; Chemoprevention; Field cancerisation; Skin toxicity; Repair balm; Clinical trial

Key Summary Points

Why carry out this study?

Local skin reactions commonly limit tolerability and completion of topical 5-fluorouracil field therapy despite its high efficacy and chemopreventive benefit.

Strategies to improve tolerability, including support of the skin barrier, remain an unmet clinical need.

This study evaluated whether adjunctive use of a prebiotic and panthenol-containing repair balm (BB5+) improves tolerability and treatment adherence.

What was learned from the study?

Adjunctive BB5+ repair balm did not significantly improve treatment completion but reduced local skin reaction severity and improved quality of life, particularly for facial field therapy.

These findings suggest that barrier repair may improve tolerability of topical 5-fluorouracil without compromising treatment exposure.

Adjunctive supportive strategies may represent a simple, accessible approach to improve patient experience during field therapy for actinic keratoses.

INTRODUCTION

Keratinocyte cancers (KCs), including basal-cell carcinoma and squamous-cell carcinoma (SCC), are the most common malignancies worldwide, with Australia having among the highest incidence rates globally. It is estimated that approximately two in three Australians will develop skin cancer in their lifetime, with keratinocyte cancers accounting for the majority of cases [1]. In parallel, actinic keratoses (AKs), which represent early intraepidermal neoplasia within the spectrum of field cancerisation, affect up to 40–60% of individuals over 40 years of age in Australia [2]. These cancers arise predominantly from

chronically sun-damaged skin through a process of field cancerisation, whereby cumulative ultraviolet exposure leads to widespread molecular and structural alterations that predispose large areas of skin to malignant transformation. The multiplicity of lesions arising within these fields is a major contributor to disease burden.

Field-directed therapies play a critical role in reducing actinic keratoses (AKs) burden and preventing progression to invasive keratinocyte carcinoma. Among available treatments, topical 5% fluorouracil (5-FU), first approved in 1962, remains among the most effective and cost-efficient field therapies for AKs [3]. Randomised controlled trials and systematic reviews consistently demonstrate clearance rates exceeding 90%, with superiority over alternatives such as imiquimod, photodynamic therapy and ingenol mebutate [4]. Importantly, 5-FU is the only topical agent shown to confer a chemopreventive benefit by significantly reducing subsequent SCC incidence [5].

Despite its efficacy, real-world effectiveness of 5-FU is limited by treatment-related local skin reactions (LSRs), including erythema, inflammation, erosion, pain and pruritus, which frequently lead to treatment interruption or early withdrawal. Evidence suggests that about half of patients may be unable to complete a full treatment course, particularly with longer regimens, thereby undermining both AK clearance and chemopreventive benefit [6]. While LSRs are well-recognised, their objective assessment has historically been inconsistent. Standardised grading systems, such as the validated scale developed by Rosen et al., provide a framework for reproducible evaluation of treatment-related toxicity and enable meaningful comparison across studies [7].

Improving tolerability of topical 5-FU without compromising efficacy is therefore of substantial clinical importance. Recent studies have reported the efficacy of a prebiotic and panthenol-containing repair balm in reducing downtime after laser treatments, as well as lesion-directed (cryotherapy) or field (daylight photodynamic therapy) treatment of actinic keratoses [8–10]. The repair balm Baume B5+ (BB5+) is a readily available barrier repair formulation containing 5% panthenol (vitamin B5),

madecassoside (a heteroside extract of *Centella asiatica*), Tribioma (a prebiotic complex), shea butter, Thermal Spring Water of La Roche-Posay (LRP-TSW) and trace elements, with these compounds exhibiting repairing, protecting, soothing, antioxidant, skin barrier enhancement, anti-inflammatory and anti-microbial properties, which can contribute to the management of various skin conditions and the promotion of overall skin well-being, due to their diverse and complementary actions [11]. Dexpantenol has demonstrated efficacy in reducing inflammation, restoring skin barrier function and accelerating epidermal repair across a range of inflammatory and iatrogenic dermatoses [11, 12]. We hypothesised that adjunctive use of BB5+ during 5-FU field therapy would reduce LSR severity, improve patient tolerability and support treatment adherence and conducted a randomised single blind clinical trial to evaluate the benefit of Baume B5+.

METHODS

Study Design and Setting

Ethical approval was obtained from the relevant Human Research Ethics Committee (HREC; HREC/2024/QMS/104804). This study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. All participants provided written informed consent prior to enrolment and for publication of clinical images, where applicable. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR; Trial Registration No. ACTRN12624000911594).

This was a single-blind, parallel-group randomised controlled trial conducted in outpatient dermatology settings in Queensland, Australia.

Participants

Adults aged ≥ 18 years attending the Princess Alexandra Hospital dermatology clinics in Brisbane, Australia, who were prescribed topical 5%

fluorouracil (5-FU) for field treatment of actinic keratoses (AKs) on the face/scalp or hands/forearms were eligible.

Exclusion criteria included hypersensitivity to 5-FU, pregnancy, known dihydropyrimidine dehydrogenase deficiency, concurrent routine topical therapies (excluding sunscreen), inability to provide informed consent or inability to comply with study procedures.

Randomisation and Blinding

Participants were randomised in a 1:1 ratio using a computer-generated sequence, stratified by treatment site (face/scalp versus hands/forearms) and immunocompetence (immunocompetent versus immunosuppressed). The allocation sequence was generated centrally.

Outcome assessors evaluating clinical photographs were blinded to treatment allocation.

Interventions

The control group applied topical 5% fluorouracil twice daily for 4 weeks, resulting in a maximum of 56 applications.

The intervention group applied topical 5% fluorouracil twice daily followed by BB5+ repair balm approximately 30 min later.

Participants in the intervention group were provided with standardised instructions on application of the repair balm, including twice-daily application after 5-FU. Adherence was prospectively monitored using daily electronic surveys with automated reminders and reinforced during weekly follow-up assessments. The quantity applied was guided by treatment surface area, reflecting routine clinical practice.

Participants using other routine topical agents (excluding sunscreen) were excluded at enrolment. During the study, participants received standard care advice consistent with routine clinical practice. All participants received counselling regarding sun protection, expected treatment reactions and the management of treatment interruptions, including guidance on resuming therapy if required.

Outcomes

The primary outcomes were:

1. Treatment adherence, defined as completion of ≥ 42 applications of 5-FU over 4 weeks. Adherence was assessed using daily participant-reported application logs collected via electronic surveys.
2. Worst local skin reaction (LSR) score during treatment, assessed using a validated severity scale. Assessments were performed at day 14 (D14), day 21 (D21) and day 28 (D28) using standardised clinical photographs, with scores determined by consensus between two investigators.

Secondary outcomes included serial LSR scores at weeks 1–4 and Dermatology Life Quality Index (DLQI) scores at weeks 2 and 4.

Statistical Analysis

The sample size was estimated on the basis of previous reports indicating a 31% completion rate of 5-FU therapy. Assuming that adjunctive BB5+ repair balm would increase completion to 62%, 37 participants per group were required to achieve 80% power at a significance level of $p < 0.05$.

Descriptive statistics were used to summarise baseline characteristics. Between-group comparisons were performed using appropriate parametric or non-parametric tests.

Analyses were conducted on participants who commenced treatment and had available outcome data (modified intention-to-treat approach), consistent with the predefined analytical framework focusing on treatment exposure and adherence.

Subgroup analyses were performed according to treatment site and immunocompetence. At each time point, analyses included only participants who were still on treatment (day 14 and day 21) or who had achieved ≥ 42 (± 4) applications at later time points. This corresponded to $n = 36$ at day 14, $n = 32$ at day 21 and $n = 25$ at day 28.

Quality-of-life impact was assessed using the DLQI for participants treated on the face, dichotomised into no-to-low impact (DLQI < 6) and moderate-to-very-large impact (DLQI ≥ 6). Groups were compared using an unpaired *t*-test with Welch's correction. Statistical significance was defined as $p < 0.05$. No interim analyses or stopping rules were prespecified.

Data Availability and Protocol

The trial protocol, statistical analysis plan, statistical code and de-identified participant data are available from the corresponding author upon reasonable request.

Patient and Public Involvement

Although this research was informed by clinical discussions and patient experiences in Queensland skin cancer clinics, there was no formal patient or public involvement in the design of the study. Participants provided feedback on treatment tolerability through daily surveys and validated patient-reported outcome measures.

Protocol Deviations

No significant changes to trial methods or outcomes occurred after trial commencement.

RESULTS

Participant Flow and Characteristics

A total of 66 patients were approached, 59 consented and 50 completed the study and could be analysed. Reasons for attrition included non-compliance and failure to commence treatment. Recruitment occurred between August 2024 and 2025. Participant flow is shown in the CONSORT diagram (Fig. 1).

Among the 50 patients, 26 were immunosuppressed and 24 immunocompetent individuals (Table 1). The mean age of the cohort was 66 years (range 44–88), with immunocompetent participants slightly older than

immunosuppressed participants (69 versus 66 years). Overall, most participants were male (74%).

Treatment sites included the face or scalp in 27 participants and the hands or forearms in 23 participants. A history of skin cancer was highly prevalent (90%, $n = 45$), affecting 25 of 26 immunosuppressed participants and 20 of 24 immunocompetent participants. Among those with prior skin cancer, a substantial proportion had a high cumulative disease burden, with 23 participants reporting a history of 20 or more skin cancers. Consistent with this, most participants had undergone repeated prior treatments for actinic damage, with 39 participants reporting five or more previous treatments for sunspots.

Previous treatment for skin cancers was common, most frequently involving the face or scalp (76%, $n = 38$) and the hands or arms (66%, $n = 33$). Cryotherapy (88%, $n = 44$) and 5-FU (74%, $n = 37$) were the most commonly reported prior treatment modalities, while photodynamic therapy, imiquimod and ingenol mebutate were infrequently used.

Prior exposure to 5-FU had occurred in the majority of participants, with 32 participants previously treated the face or scalp and 18 on the hands or forearms. Among those previously treated with topical 5-fluorouracil, 26 participants had completed a full treatment course, while 11 had not. The most commonly reported reason for incomplete treatment was inability to tolerate therapy (16%, $n = 8$), providing relevant context for the tolerability, adherence and local skin reaction outcomes reported subsequently (Tables 2, 3).

Treatment Adherence and Completion

Patients were considered to have adhered to treatment if a minimum of 42 applications were completed over the 4-week treatment period. Overall, 28 patients (56%) completed the 42 applications (Table 2). A slightly higher proportion of participants in the BB5+ repair balm group achieved the predefined adherence threshold (59% [16/27]) compared with standard of care (SOC) (52% [12/23], non-significant). The mean number of applications completed

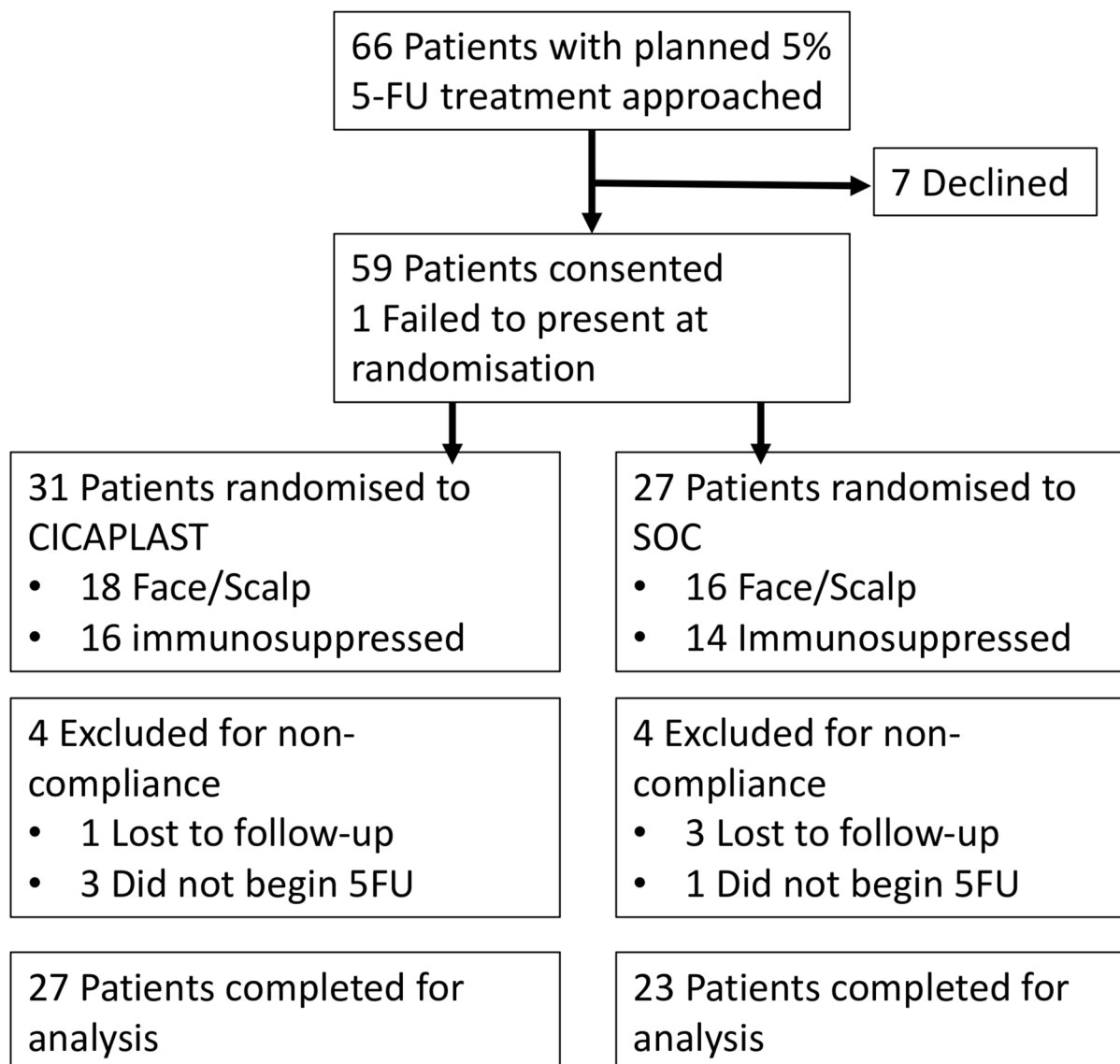


Fig. 1 Study flow chart. Flow diagram showing patient recruitment, randomisation, exclusions and final numbers included in the analysis. Of 66 patients approached for planned 5% 5-fluorouracil (5-FU) field therapy, 59 consented, and 58 were randomised to either BB5+ or

standard of care (SOC). Exclusions due to non-compliance, loss to follow-up, or failure to commence treatment are detailed, with 27 patients in the BB5+ group and 23 patients in the SOC group completing the study and included in the final analysis

was identical between the BB5+ repair balm and the SOC groups (mean 39.6 versus 39.9 applications, non-significant).

Among participants treated on the face, a higher proportion in the intervention group achieved ≥ 42 applications compared with SOC (60% [9/15] versus 42% [5/12]). In contrast, adherence rates for treatment of the hands and

forearms were similar between groups (58% [7/12] intervention versus 64% [7/11] SOC).

Among immunosuppressed participants, a greater proportion in the intervention group completed ≥ 42 applications compared with standard of care (57% [8/14] versus 42% [5/12]). Completion rates among immunocompetent participants were comparable between groups

Table 1 Characteristics

Variable	All (n = 50)	Immunosuppressed (n = 26)	Immuno-competent (n = 24)
Age (mean)	66 (44, 88)	66	69
Sex			
Male	37 (74%)	23	14
Female	13 (26%)	3	10
Treatment area			
Face/scalp	27	15	12
Hands/arms	23	11	12
Previously treated for skin cancer			
No	5	1	4
Yes	45	25	20
No. of skin cancers previously treated			
1	1	1	0
2–9	11	8	3
10–19	8	6	2
20+	23	9	14
Missing data	7		
Past skin cancer areas treated			
Face/scalp	38	21	17
Hands/arms	33	15	18
None of the above	1	0	1
Previously treated for sun spots			
Never	3	0	3
1–5 times	8	4	4
5+ times	39	21	18
Types of treatment for skin cancer or sunspots			
Fluorouracil/5-FU	37	23	14
Cryotherapy	44	24	20
Photodynamic therapy	2	1	1
Ingenol mebutate	1	0	1
Imiquimod	3	2	1

Table 1 continued

Variable	All (n = 50)	Immunosuppressed (n = 26)	Immuno-competent (n = 24)
Areas previously treated with 5-FU			
Face/scalp	32	20	12
Hands/arm	18	11	7
Completed full course treatment of 5-FU			
Yes	26	18	8
No	11	5	6
Reason for incomplete course treatment			
Unable to tolerate treatment	8	4	4
Other	3	1	2

Table 2 Primary outcomes over 4 weeks of topical 5% fluorouracil treatment (n = 50)

Outcome	BB5+ group (n = 27)	Standard of care (SOC) (n = 23)
Patients achieving ≥ 42 applications, n (%)	Overall	16 (59%)
	Treatment field	9/15 (60%)
	Face (n = 27)	7/12 (58%)
	Hands/forearms (n = 23)	5/12 (42%)
	Immune status	7/11 (64%)
	Immunocompetent (n = 24)	8/14 (57%)
Average number of applications	Immunosuppressed (n = 26)	5/12 (42%)
	Immunocompetent (n = 24)	7/11 (62%)
		39.6 \pm 3.1
		39.9 \pm 2.9

(62% [8/13] intervention versus 64% [7/11] standard of care).

Overall, although these differences did not reach significance, it was important to note that treatment completion in the absence of BB5+ repair balm seemed to be more likely on the forearms and hands and among immunocompetent patients as opposed to the applications on the face or among immunosuppressed patients. In contrast, this pattern was not observed in the BB5+ group, where completion rates were similar across anatomical sites and immune status.

Assessment of Skin Reactions

LSR scores (out of a maximum of 20) were evaluated at day 14 (D14), day 21 (D21) and day 28 (D28) in person and based on standardised clinical photographs (Fig. 2A) independently reviewed by dermatologists blinded to treatment allocation. Across all time points, severity scores demonstrated a progressive increase over the treatment course, consistent with the known cumulative inflammatory effects of topical 5-FU. Mean scores increased from 7.44 at D14

Table 3 Local skin reaction scores at each time point

Outcome	BB5+	Standard of care (SOC)	p-Value
D14 ^a	6 ± 0.5	8.4 ± 1.2	0.0435
D21	7.1 ± 0.7	10.8 ± 1.1	0.0054
D28	7.2 ± 0.8	9.4 ± 1.3	0.0787
Mean worst LSR severity score ^b (range)	9.2 (5–18)	10.2 (2–17)	NS

^aOnly those patients still under treatment or with near completion (42 ± 4 applications) of therapy were considered at each time point

^bWorst local skin reaction (LSR) severity score assessed during treatment using the Rosen et al. grading scale (maximum score 20). Assessments were based on standardised clinical photographs reviewed by dermatologists blinded to treatment allocation

to 8.47 at D21, before stabilising at 7.84 by D28 (Fig. 2B) ($p=0.08$, ANOVA). For each time point, we only considered those still on treatment (or those who had completed 42 ± 4 applications). There were significant (up to 35%) reductions in LSR scores in patients treated with BB5+ repair balm as compared with SOC (Fig. 2C). This was particularly true at D14 (6 versus 8.4, $p=0.04$; Table 3) and D21 (7.1 versus 10.8, $p=0.005$). At D21, BB5+ repair balm improved the LSR on the face ($p=0.0114$) and to a lesser extent on forearms ($p=0.058$) (Fig. 2D). Participants in the BB5+ repair balm group experienced a lower mean worst LSR score during treatment compared with those receiving standard of care (mean 9.2 ± 0.6 [range 5–18] versus 10.2 ± 1.0 [range 2–17]), despite similar cumulative exposure to fluorouracil. This was mainly due to stabilisation of scores in the final week of treatment.

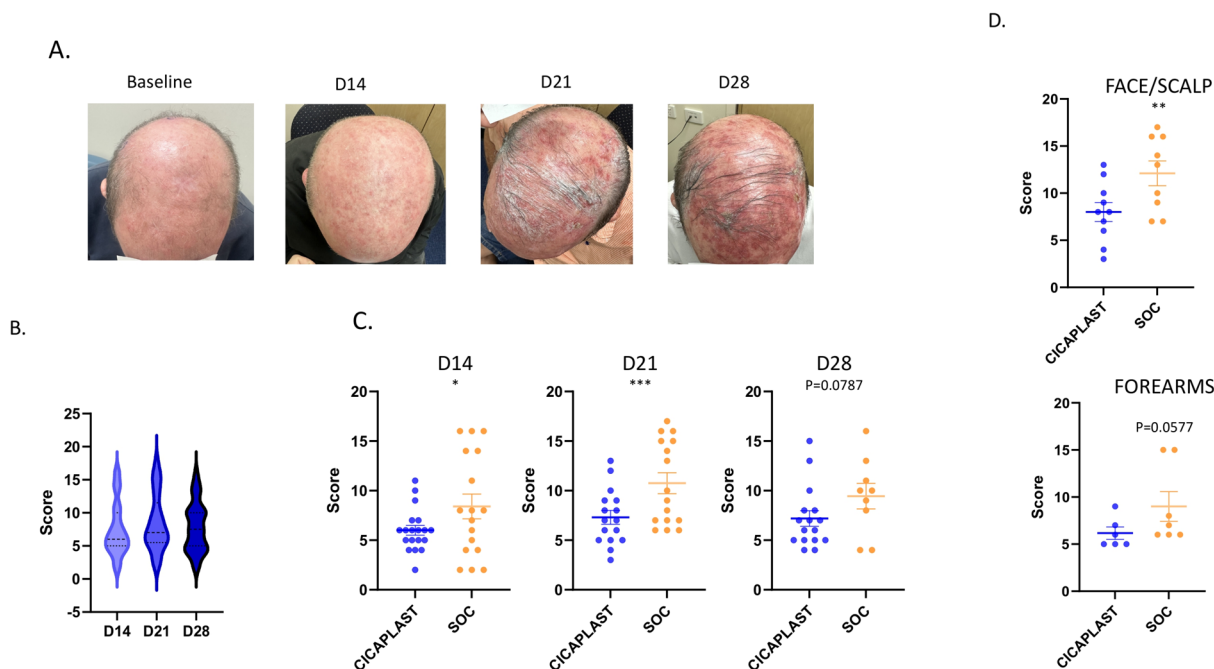


Fig. 2 Assessment of treatment-related skin reactions during 5-fluorouracil field therapy. **a** Representative clinical photographs of the scalp at baseline and days 14, 21 and 28 following treatment initiations. **b** Distribution of clinician-assessed skin reaction severity scores at days 14, 21 and 28 based on clinical photography. **c** Comparison of severity scores between the BB5+ and SOC groups at

days 14 ($n=34$), 21 ($n=32$) and 28 ($n=25$). **d** Effect of intervention on severity scores stratified by treatment site (face/scalp and forearms). Data are presented as individual data points with mean ± standard error. p -Values indicate between-group comparisons using unpaired t -test with Welch correction. * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$

Quality of Life Assessment

Using the DLQI method there was notable alteration of quality of life, particularly in the second fortnight of the treatment (Fig. 3A). We did not observe any significant effect of BB5+ repair balm at D14 and D28 when considering all patients (Fig. 3B). However, given our previous findings of the site-specific significant effects, we focused on those patients who applied fluorouracil to the face/scalp (Fig. 3).

Among participants who used 5-FU to the face/scalp, BB5+ repair balm was associated with a significantly lower proportion of patients experiencing moderate to high DLQI impact at both time points. At day 14, BB5+ repair balm use was significantly protective ($p=0.0081$) with no patient displaying a DLQI score of 6 or more

(Table 4; Fig. 3C). This effect was sustained at day 28 and those with BB5+ repair balm had four times fewer likelihood to have moderate to high alterations of their quality of life by the therapy (relative risk [RR] 0.23, 95% confidence interval [CI] 0.04–0.87; $p=0.0498$).

DISCUSSION

Local skin reactions remain a major determinant of tolerability and adherence to topical 5-fluorouracil (5-FU) field therapy for actinic keratoses. Contemporary Australian and New Zealand guidance emphasises the importance of structured pre- and post-treatment skin care to support patients undergoing field-directed therapies, particularly in high-burden and high-risk

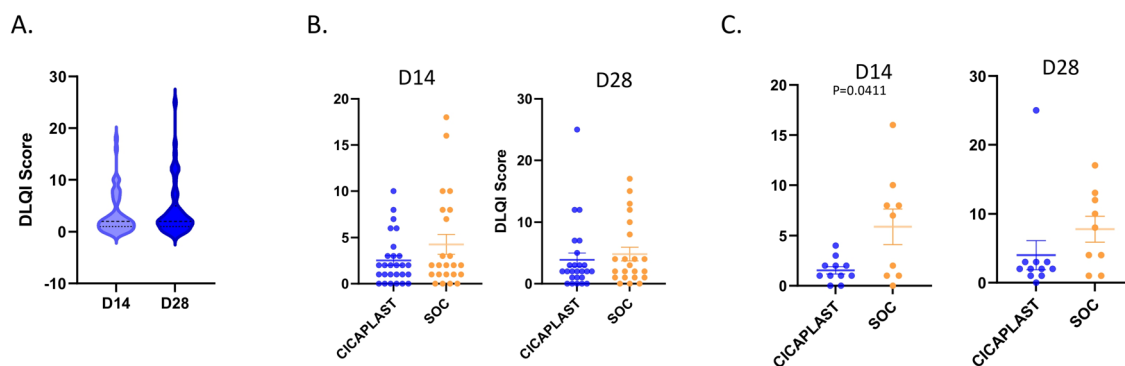


Fig. 3 Patient-reported quality-of-life outcomes assessed using the Dermatology Life Quality Index (DLQI). **a** Distribution of DLQI scores for the total cohort at days 14 and 28. **b** Comparison of DLQI scores between the BB5+ and standard of care (SOC) groups at days 14 ($n=50$) and 28 ($n=47$). **c** Subgroup analysis comparing DLQI scores

between treatment groups for face/scalp field therapy at days 14 ($n=20$) and 28 ($n=20$). Data are shown as individual data points with mean \pm standard error. Reported p -values reflect between-group comparisons using unpaired t -test with Welch's correction. $p < 0.05$ is indicated by an asterisk (*)

Table 4 Dermatology Life Quality Index (DLQI) outcomes for facial field treatment with topical 5% fluorouracil

Population	Time point	Group	DLQI < 6 (no-to-low impact), n (%)	DLQI \geq 6 (moderate-to-high impact), n (%)	Effect estimate
Facial participants completing ≥ 42 applications (± 4)	Day 14	BB5+	11/11 (100%)	0/11 (0%)	$p=0.0081$
		SOC	4/9 (44%)	5/9 (56%)	
	Day 28	BB5+	10/11 (91%)	1/11 (9%)	RR 0.23 (95% CI 0.04–0.87), $p=0.0498$
		SOC	4/9 (44%)	5/9 (56%)	

populations [13]. Similarly, expert consensus derived from modified Delphi methodologies has highlighted optimisation of tolerability as a key unmet need in actinic keratosis management, with adjunctive supportive measures increasingly recognised as integral to treatment success [14, 15].

In this randomised study evaluating adjunctive use of a prebiotic and panthenol containing repair balm (BB5+ repair balm) during topical 5% fluorouracil field therapy, the intervention was associated with improved tolerability, as reflected by a significant reduction in local skin reaction severity and improved quality of life, even if it only marginally affected overall treatment adherence. Although a modestly higher proportion of participants in the intervention group completed ≥ 42 applications, the absolute difference between groups was small and the mean number of applications was identical, and therefore the primary outcome of the trial was not met. These findings underscore the persistent challenge of maintaining adherence to prolonged fluorouracil regimens, even when adjunctive supportive care is provided.

Importantly, BB5+ repair balm was associated with a 35% reduction in LSR scores. Peak inflammatory toxicity is a key driver of patient discomfort and treatment dissatisfaction, and attenuation of these reactions may represent a clinically relevant benefit even in the absence of improved completion rates, and this was reflected in the worst score that also trended down. Reduced severity of peak reactions may improve patient experience, willingness to re-engage with future field therapy and acceptability of fluorouracil in routine practice. Of significant interest, exploratory subgroup analyses suggested that the potential adherence benefit of adjunctive therapy may be context-specific. LSR scores were particularly improved on the face/scalp as opposed to forearms and hands. Similarly, quality of life was improved by BB5+ repair balm when the treatment was targeted to the face/scalp. Improved completion rates were observed for facial treatment fields reaching levels observed on forearms where 5-FU is classically better tolerated. We also observed more reactions among immunosuppressed patients where BB5+ repair balm provided significant benefits. In contrast, no

adherence benefit was observed for acral sites or immunocompetent participants, highlighting the multifactorial nature of treatment adherence. These subgroup findings are clinically plausible but should be interpreted cautiously given the limited sample size and exploratory nature of the analyses. The study was not powered to detect statistically significant differences in adherence across subgroups, and the results should be considered hypothesis-generating. Overall, these secondary outcomes support the role of adjunctive prebiotic and panthenol-containing repair balm in improving patient-reported quality-of-life outcomes during topical fluorouracil therapy, particularly for facial field treatment.

Prior studies evaluating adjunctive emollient use alongside topical 5-FU have demonstrated reductions in the severity of local skin reactions without compromising treatment efficacy. In a single-blind randomised trial, Stockfleth et al. reported significantly lower local skin reaction severity with concurrent emollient use compared with 5-FU alone [16]. These findings align with the present study, in which adjunctive BB5+ repair balm was associated with reduced local skin reaction severity, particularly during peak inflammatory phases and in facial field therapy.

The biological plausibility of barrier repair as an adjunct to inflammatory dermatologic treatments is further supported by dermocosmetic studies demonstrating improved skin recovery and reduced downtime following procedural interventions [9–11]. A randomised double-blind intra-individual study evaluating the same BB5+ repair balm intervention showed significantly improved skin recovery compared with standard repair skincare following fractional CO₂ laser treatment [8, 9, 17]. Collectively, these data support the role of targeted barrier repair formulations in mitigating treatment-related cutaneous inflammation and supporting patient experience.

Our study was limited by the high proportion of participants who had already used topical fluorouracil, potentially narrowing the analysis to those with good tolerance of the treatment. This is reflected in a high proportion of those completing treatment (52–59%) compared with 31% reported

previously [3] and may partly explain why BB5+ repair balm did not significantly increase overall treatment completion in this cohort. The study also did not reach the prespecified sample size and was therefore underpowered to detect differences in treatment completion rates, which may further explain the lack of statistical significance observed for the primary endpoint despite consistent trends favouring the intervention. In addition, analyses were conducted using a modified intention-to-treat approach, including only participants who commenced treatment and had available outcome data, which may introduce bias and limit generalisability. The single-blind design may also introduce assessment bias. While this pragmatic approach reflects real-world treatment exposure, including variability in topical product use during treatment, it may also introduce unmeasured confounding. Furthermore, several outcomes did not reach statistical significance, and subgroup analyses were exploratory and hypothesis-generating. Despite these limitations, improvements in local skin reaction severity and quality of life suggest a clinically meaningful benefit, particularly for facial field therapy where tolerability is a critical determinant of adherence. These findings are consistent with expert consensus recommendations advocating proactive management of local skin reactions to optimise patient-centred outcomes during actinic keratosis treatment [13–15].

CONCLUSIONS

In this randomised trial, adjunctive BB5+ repair balm did not significantly improve overall treatment completion but was associated with reduced peak local skin reaction severity and improved quality of life, particularly for facial field therapy. These findings suggest that barrier repair may improve tolerability of topical fluorouracil and enhance patient experience during treatment.

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validation, visualisation and writing—original draft preparation. Regina Yu: investigation, data curation, methodology, project administration, resources and writing—review and editing. Susan Brown: methodology and project administration. Nicholas Muller: investigation and data collection. Samuel X. Tan: investigation and data collection. Edwige Roy: formal analysis. Suzanne Nguyen: conceptualisation, data curation, funding acquisition, methodology and resources. Delphine Kerob: conceptualisation, data curation, funding acquisition and methodology resources. Kiarash Khosrotehrani: conceptualisation, data curation, formal analysis, funding acquisition, project administration, resources, software, supervision, validation, visualisation and writing—review and editing.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of Interest. Kiarash Khosrotehrani has received consultancy and speaking fees from La Roche-Posay for unrelated projects. Suzanne Nguyen is employed by La Roche-Posay Laboratoire Dermatologique. Delphine Kerob is employed by La Roche-Posay Laboratoire Dermatologique. Anne Tseng, Regina Yu, Susan Brown, Nicholas Muller, Samuel X Tan and Edwige Roy have nothing to disclose.

Ethical Approval. Ethical approval was obtained from the relevant Human Research Ethics Committee (HREC; HREC/2024/QMS/104804). This study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. All participants provided written informed consent prior to enrolment and

for publication of clinical images. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR; Trial Registration No. ACTRN12624000911594).

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