



Efficacy and safety of topical cream containing aminoacyl tRNA synthetase complex interacting 1-derived peptide in mitigating radiation dermatitis after adjuvant radiotherapy for breast cancer

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Abstract

Purpose Acute radiation dermatitis (ARD) is a frequent side effect experienced by breast cancer patients undergoing radiotherapy. This study aimed to assess the efficacy and safety of a topical cream containing aminoacyl tRNA synthetase complex interacting 1 (AIMP1)-derived peptide (AdP) in mitigating radiation dermatitis (RD) in breast cancer patients undergoing radiotherapy.

Methods An 8-week single-center, prospective pilot study was conducted to compare the clinical efficacy and safety of an AdP-containing cream with a control cream lacking AdP for the mitigation of RD. Fifteen patients undergoing radiotherapy applied the test cream to the right side and the control cream to the left side of the radiation exposure site, bisected by the nipple line. RD was evaluated at baseline and at weeks 2, 4, 6, and 8, employing the 5-point grading system advocated by the Radiation Oncology Group (RTOG).

Results The average RTOG score was lower on the test side in comparison to the control side, and a less pronounced increase in melanin index was observed on the test side. However, these differences were not statistically significant. Both sides exhibited increased skin hydration and decreased transepidermal water loss. Analyzing the maximum RTOG scores throughout the study, RD of maximum grades 1 and 2 was noted in 54.5% and 45.5% of patients on the test side. On the control side, the maximum grades 1 and 2 were observed in 45.5% and 54.5% of patients respectively.

Conclusion The AdP-containing cream did not prove to be more effective than the control cream without AdP in mitigating RD. However, the total incidence of RD in our study was notably lower than previously documented, illustrating the protective effects of both the test and control creams.

Keywords AIMP1-derived peptide (AdP) · Breast cancer · Radiation dermatitis (RD) · Topical cream

Introduction

Acute radiation dermatitis (ARD) represents a the most common serious side effect in breast cancer patients undergoing radiotherapy (RT) because the skin is the first organ exposed to radiation [1]. Although there has been significant progress in treatment approaches utilizing modern technology and fractionated schedules, radiation-induced skin injuries persist as a frequent occurrence in cancer patients [2]. It is known that moderate-to-severe skin reactions occurs in approximately 95% of patients treated with RT, and most notably in those with head and neck cancer and breast cancer [3–7].

ARD has a major impact on the quality of life (QOL) of cancer patients undergoing RT, and may even interfere with their treatment, thus potentially reducing their effect

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[8]. While mild ARD may be symptomatically managed with topical emollients, its severe form can cause considerable discomfort, limit daily activities, and may even necessitate interruptions in treatment [9]. Moreover, severe radiation dermatitis (RD) leads to increased fibrosis and pigmentation, adversely affecting both cosmetic outcomes and the QOL following breast-conserving surgery, or can even result in serious complications such as sepsis [10]. Despite the high prevalence and impact of RD on cancer treatment outcomes, there is a lack of definite recommendations on its prevention and treatment [8, 11, 12]. An abundance of literature regarding numerous pharmacological and non-pharmacological treatments for RD prophylaxis and management have been published, yet there is no consensus to date regarding the gold standard treatment [5, 8, 13–16].

A European-American study showed that therapeutic skin care often relies on anecdotal reports rather than evidence [17], similar observations were also seen by the British radiation oncologists [18], as well as in German speaking radiation oncology community [17–21]. Most recently, the clinical practice guidelines for the prevention and management of ARD suggested by Multinational Association of Supportive Care in Cancer (MASCC) based on international Delphi consensus-based recommendations also concluded that most interventions were not recommended due to insufficient evidence, conflicting evidence, or lack of consensus to support use, suggesting the need for further research [12].

However, prophylactic, and early management of ARD not only decrease the severity of skin reactions but also the incidence of late onset RD which can significantly reduce patients' QOL [22, 23]. Therefore, although it is impossible to completely prevent RD, it is crucial to identify strategies to mitigate RD. The aminoacyl tRNA synthetase complex interacting 1 (AIMP1)-derived peptide (AdP) emerges as a novel cosmeceutical ingredient employed for skin aging and whitening [24, 25]. Research has revealed the potential of AdP in enhancing skin repair through mechanisms such as fibroblast proliferation, collagen regeneration, and improved wound healing [26, 27]. Based on these findings, we conducted a prospective single-center pilot study to assess the efficacy and safety of AdP-containing cream in mitigating RD in breast cancer patients receiving RT.

Materials and methods

Study design and patient enrollment

An 8-week prospective, single-center pilot study was conducted to evaluate the clinical efficacy and safety of a cream containing AdP (Easydew MD regen cream, CGBIO co., Ltd, Seoul, Korea) in comparison to a control cream without AdP (Easydew MD cream, CGBIO Co.,

Ltd, Seoul, Korea). The objective was to assess mitigation of RD in breast cancer patients receiving RT. The study received approval from the Institutional Review Board of Chung-Ang University Hospital (IRB No. 2205–002–505) and was conducted in accordance with the CONSORT 2010 guidelines.

A total of fifteen patients, aged between 19 and 80, diagnosed with breast cancer and having undergone breast conservation surgery (BCS) with planned adjuvant RT were enrolled. Inclusion criteria included unilateral breast cancer with no skin tumor invasion and successful completion of BCS, with or without adjuvant chemotherapy, followed by a planned course of RT. The design of this trial is depicted in Supplementary Fig. 1.

Radiation therapy

The study employed an accelerated hypofractionation scheme, informed by the Whelan et al. trial [28]. The radiation schedules implemented were either 4,050 or 4,320 cGy, administered in 15 or 16 fractions with 6MV photon beam, supplemented by a boost irradiation of 1000 cGy with electron beam. The cumulative radiation dosage amounted to 5050 or 5320 cGy. All patients received ipsilateral whole breast irradiation (WBI) using forward-planned intensity-modulated radiation therapy technique. Irradiation was conducted using a Varian 21EX Linear Accelerator (LINAC; Varian Medical Systems, Palo Alto, CA).

Intervention protocol

During the initial visit, each patient received two distinct creams: a test cream containing AdP and a control cream, identical to the test cream but without AdP. A detailed breakdown of the specific compositions of both the test and control creams can be found in Table 1. The site of radiation exposure was bisected by the nipple line, with patients directed to apply the test cream to the right side and the control cream to the left side of the nipple line. The designated creams were administered starting the night prior to the initiation of RT, continuing until two weeks following the conclusion of RT. The prescribed application was twice daily, once in the morning and once in the evening during each patient's general skin care routine, everyday including RT and non-RT days. Throughout the study period, patients were explicitly guided to refrain from using any topical agents, such as corticosteroids, other immunomodulators, or moisturizers, that could potentially interfere with the trial's evaluation. Compliance with the cream application protocol was assessed daily by the treating radiation oncologist.

Table 1 Compositions of Easydew MD cream (control cream) and Easydew MD regen cream (test cream)

Easydew MD cream (control cream)	Easydew MD regen cream (test cream)
1.Purified water	1.Purified water
2.Glycerin	2.Glycerin
3.Disodium EDT	3.Disodium EDT
4.Xanthan gum	4.Xanthan gum
5.Carbomer	5.Carbomer
6.Sodium Hyaluronate	6.Sodium Hyaluronate
7.Glyceryl Stearate	7.Butylene Glycol
8.Polyethylene Glycol (100) Stearate	8.Glyceryl Stearate
9.Squalane	9.Polyethylene Glycol (100) Stearate
10.Dimethicone	10.Squalane
11.Serisin	11.Dimethicone
12.Gamma-Linolenic Acid	12.Seresin
13.Cholesterol	13.Gamma-Linolenic Acid
14.1,2-hexanediol	14.Cholesterol
15.Ceramide	15.1,2-Hexanediol
16.Caprylic/capric triglyceride	16.Ceramide NP
17.1,3-butylene glycol	17.Caprylic/Capric Triglyceride
18.Tocopheryl Acetate	18.Tocopheryl Acetate
19.Potassium Hydroxide	19.Potassium Hydroxide
	20.SH-Oligopeptide-5SP

Clinical outcome assessment

The evaluation was conducted at specific time intervals: baseline, week 2, week 4, week 6, and week 8. The primary outcome was the alteration in RD score, using the Radiation Oncology Group (RTOG) recommended 5-point grading system at weeks 2, 4, 6, and 8 in comparison to the baseline (Table 2) [29]. The RTOG grading was performed by an experienced dermatologist and was double checked by an experienced radiation oncologist.

Secondary outcomes encompassed changes in biophysical parameters, including the erythema and melanin indices as assessed by Mexameter® MX 18 (Courage & Khazak, Cologne, Germany), transepidermal water loss (TEWL) as gauged by Tewameter® TM 300 (Courage & Khazak, Cologne, Germany), and skin hydration as determined by Corneometer® CM 825 (Courage & Khazak, Cologne, Germany). Previous studies have shown that quantitative biophysical measurements of the skin are advantages because it enables detection of changes in skin with higher sensitivity to assess changes that are undetectable by a visual assessment or palpation [30]. Patients were advised against the application of cosmetics or washing the measurement site within two hours preceding the measurements. The same

investigator conducted all measurements in a controlled environment with constant temperature (23 °C) and humidity (45%). Other secondary outcomes included variations in subjective evaluation of pruritus and pain, quantified using a visual analog scale (VAS). Adverse events were meticulously evaluated by a dedicated investigator, with patients mandated to report any adverse occurrences during both treatment and follow-up periods.

Statistical analysis

Categorical variables (such as itching sensation, pain, RTOG, and IGA scores) were presented in terms of frequencies and proportions, while continuous variables (including erythema index, melanin index, TEWL, and skin hydration) were described as means and SDs with a $p < 0.05$ considered statistically significance. Various statistical methodologies, including descriptive statistics, Wilcoxon signed-rank test, McNemar's test, McNemar-Bowker test, and linear mixed-effect analysis, were employed. The analyses were executed using R language version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and T&F software version 4.0 (YooJin BioSoft, Korea).

Table 2 The Radiation Oncology Group (RTOG) scale for skin toxicity

Grade	Description
RTOG 0	No change over baseline
RTOG 1	Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating
RTOG 2	Tender or bright erythema, patchy moist desquamation, moderate oedema
RTOG 3	Confluent, moist desquamation other than skin folds, pitting oedema
RTOG 4	Ulceration hemorrhage, necrosis

Results

Patient characteristics

A total of fifteen patients were assessed for eligibility, all of whom met the criteria and were consequently included in the study. Out of these, four patients were lost during the study period, leaving eleven patients for the final analysis. The patients' mean age was 56.33 ± 11.36 years, with a range of 43 to 75 years. Six patients (54.5%) received hormonal therapy, five patients (45.5%) received chemotherapy and one patient with HER-2 positive disease additionally received trastuzumab-based therapy.

Changes of RTOG score in radiation dermatitis grade (Fig. 1)

At baseline, all patients exhibited grade 0 skin toxicity. The RTOG scores were observed to peak at week 6, aligning with the point at which the effects of radiation treatment were most cumulative. Throughout the study duration, no patients reported acute toxicity grading scores of 3 or 4. At week 4, on the test side, two patients (16.7%) showed no skin toxicity, eight patients (66.7%) showed grade 1, and two patients (16.7%) exhibited grade 2 skin toxicity. Conversely, on the control side, 11 patients (91.7%) exhibited grade 1, while one patient (8.33%) exhibited grade 2 skin toxicity. At week 6, both sides saw eight patients (66.7%) with grade 1 and four patients (33.3%) with grade 2 skin toxicity. By week 8, on the test side, four patients (36.4%) exhibited no toxicity, six patients (54.5%) reported grade 1, and one patient (9.09%) reported grade 2 skin toxicity. On the control side, two patients (18.2%) reported no toxicity, and nine patients (81.8%) displayed grade 1 skin toxicity. Although the change in RTOG grade between the two groups was not

statistically significant, the mean RTOG score was slightly lower on the test side (0.73) compared to the control side (0.82) at week 8. Additionally, the distribution of the RTOG acute toxicity grading scale at week 8 indicated favorable results for the cream containing AdP.

In a comparison of the maximum RTOG scores over the course of the study, the RD of the maximum grades of 1 and 2 were observed in 54.5% (6/11) and 45.5% (5/11) of cases on the test side. On the control side, these figures were mirrored at 45.5% (5/11) and 54.5% (6/11) respectively (Table 3).

Change in melanin index (Fig. 2)

On both the test and control sides, the melanin index increased over time relative to the baseline. Notably, the degree of increase in the melanin index on the test side was less pronounced when compared to the control side (Fig. 2a). Consequently, the absolute difference in the change in melanin index from baseline between the control and test sides (calculated as the change in melanin index of control side minus test side at each time point) gradually increased over time, which means that the increase in pigmentation was much less on the test side compared to the control side, and that this difference between the test and control side became more pronounced over time. However, these changes were not found to be statistically significant (Fig. 2b) ($p=0.148$).

Change in erythema index (Fig. S2)

For both the test and control sides, the erythema index showed an increase over time (Fig. S2a). Furthermore, no difference was observed in the degree of increase in the erythema index between the two sides. Thus, there was no discernible trend in the absolute difference in erythema index between the control and test sides (Fig. S2b).

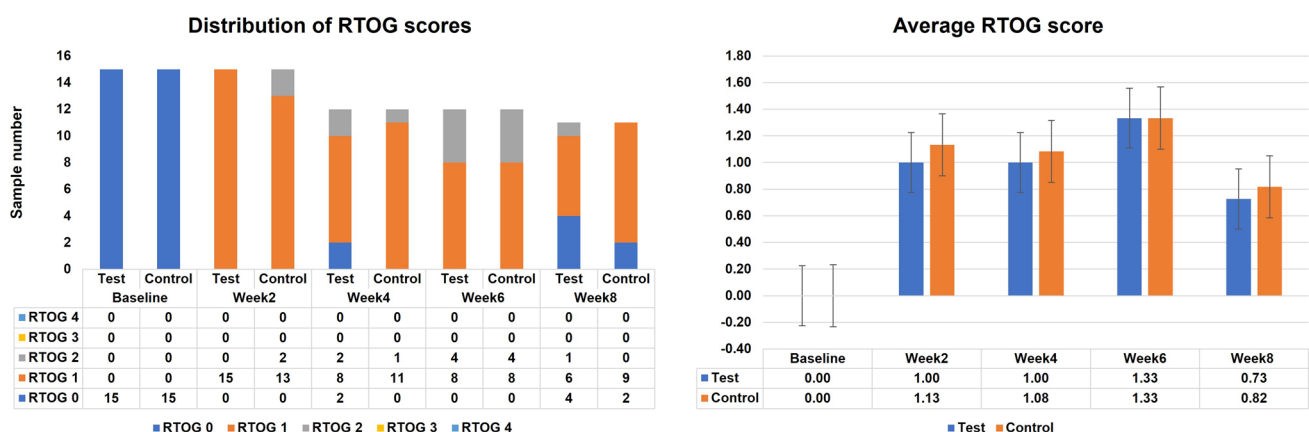
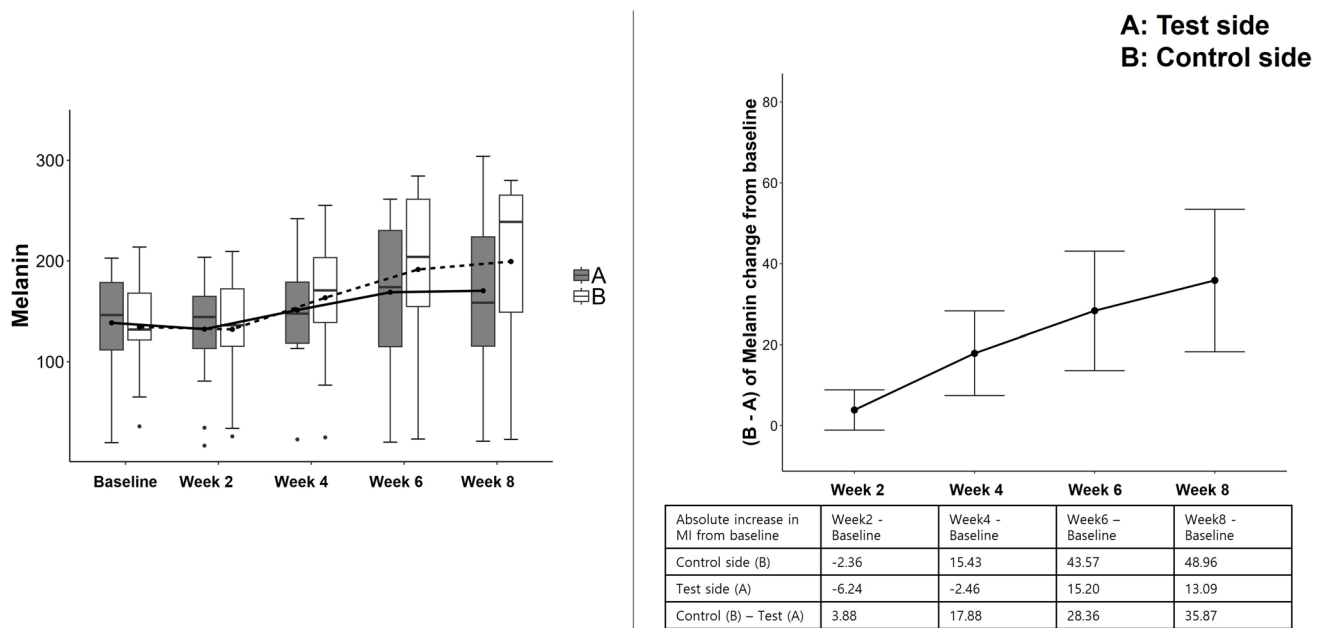


Fig. 1 Change in the distribution of the radiation dermatitis score (a), and change in the average radiation dermatitis score (b) measured using the 5-point grading system suggested by the RTOG

Table 3 The results of maximum pain scores and RTOG scores in our study compared to previous study using EGF-based cream for mitigation of RD

Variable	AdP containing cream (Easydew MD regen cream) (n = 11)	Control cream (Easydew MD cream) (n = 11)	Human Epidermal Growth Factor (EGF)-based cream (n = 20)	Control (General supportive skin care) (n = 20)
Maximum pain score (0–10)	2.45	2.54	2.80	3.13
Range	0–7	0–7	0–6	0–7
Standard deviation	± 2.02	± 2.07	± 1.67	± 1.61
Maximum RTOG Scores				
0				
1	54.5% (6/11)	45.5% (5/11)	30% (6/20)	10% (2/10)
2	45.5% (5/11)	54.5% (6/11)	55% (11/20)	50% (10/20)
3	0% (0/11)	0% (0/11)	15% (3/20)	40% (8/20)
4	0% (0/11)	0% (0/11)	0% (0/20)	0% (0/20)

**Fig. 2** Change in the melanin index (a), and change in the absolute difference in melanin index between the control and test sides (b)

Change in skin hydration and TEWL (Figs. S3 and S4)

Skin hydration exhibited an increase over time on both sides (Fig. S3a). The enhancement in skin hydration was more marked on the test side compared to the control side, causing the absolute difference in skin hydration between the two sides to diminish over time (Fig. S3b). In contrast, TEWL diminished over time on both the test and control sides (Fig. S4).

Scores for patients' pain and pruritus (Figs. S5 and S6)

Evaluating the pain score posed challenges at baseline as some patients reported experiencing pain at the surgical site. Though we specifically requested patients to assess only the stinging or burning sensations on the skin, distinguishing between pain attributed to RD and surgical site pain proved challenging. These complications were mirrored in

the baseline pain scores measured before RT, with average scores deviating from 0. Supplementary Fig. 5 illustrates a gradual decrease in pain on both sides over time, with all but two patients reporting a VAS pain score of 0 at week 8. However, no statistically significant difference was observed in the pain variations over time between the control and test sides.

Regarding pruritus scores, although the majority of patients did not report any sensation of itching, those who did experienced the most severe itching during weeks 4 and 6, coinciding with the peak cumulative effect of the radiation treatment. There was no statistically significant difference in the change in itching sensations over time between the control and test sides.

Safety

Both the AdP-containing cream (Easydew MD regen cream) and the cream without AdP (Easydew MD cream) were well tolerated by the patients. No adverse events related to the application of either cream were reported.

Discussion

RD represents a significant side effect of adjuvant RT in the treatment of breast cancer, with serious implications for a patient's quality of life [29]. The underlying pathophysiology of RD is characterized by the production of free radicals that cause DNA damage, followed by the recruitment of inflammatory cells and resultant tissue injury [31]. The healing mechanisms of RD remain incompletely understood; however, key processes are recognized to include epidermal regeneration, fibroblast proliferation, and collagen deposition [32].

The concept of “wound healing” is central to the recovery from RD, and as such, growth factors like epidermal growth factors (EGF) have been investigated for preventing this condition [33, 34]. Research has found that the prophylactic application of EGF-based cream is effective in averting RD [33]. Nevertheless, EGF is deemed a contentious cosmetic ingredient due to concerns over safety, particularly related to its potential cancer-enhancing properties [35–38]. Additionally, various studies have examined the potential of different compounds—such as aloe vera, hyaluronic acid, sucralfate, bialfine, ascorbic acid, silver sulfadiazine, moisturizing durable barrier cream, and calendula—to identify suitable topical agents that can mitigate acute RD. However, these studies have yielded inconsistent results [33, 39, 40].

In this study, the efficacy of a cream containing AdP was assessed in the prevention of RD. Aminoacyl-tRNA synthetase (ARSs) plays a crucial role in linking specific amino acids to their respective tRNAs. Among the ARS family,

nine ARSs constitute the multi-synthetase complex (MSC) in higher eukaryotes, complemented by three non-enzymatic factors: aminoacyl-tRNA synthetase complex-interacting multifunctional proteins (AIMP)1, AIMP2, and AIMP3 [41]. Notably, AIMP1 has demonstrated rapid wound healing effects in mouse models [42, 43] and has been implicated in promoting the proliferation of bone marrow-derived mesenchymal stem cells [44]. Among various fragments of AIMP1, AIMP1-derived peptide (AdP), specifically the amino acid region 6–46 induces fibroblast proliferation, and thus has been formulated as a cosmeceutical ingredient [44].

Previously conducted in vitro assays revealed that AdP treatment stimulated collagen I synthesis and fibroblast proliferation in human fibroblasts, exhibiting superior efficacy when compared to EGF. Additionally, AdP suppressed melanin synthesis by regulating tyrosinase activity, with a more potent effect than that of arbutin, a commonly used whitening cosmetic ingredient [25]. In a separate in vivo investigation evaluating AdP's impact on skin wound repair in rat models, the findings indicated that AdP enhanced re-epithelialization and collagen regeneration, downregulated inflammatory cytokines in a dose-dependent manner, and facilitated fibroblast proliferation, migration, and differentiation. AdP also demonstrated nitrite and reactive oxygen species scavenging capabilities [45]. Safety assessments confirmed the suitability of AdP as a cosmeceutical ingredient, revealing no cytotoxic or pro-inflammatory effects, with stability over three months at temperatures of −20, 4, and 20 °C [25]. Unlike EGF or other growth factors, AIMP1 exhibited anti-tumorigenic activity, further substantiating its potential in therapeutic applications [46].

The findings of this study demonstrate that the cream containing AdP does not outperform the control cream without AdP in mitigating radiation-induced skin toxicity. Contrarily, the cumulative incidence of RD following breast RT was lower in our investigation compared to previous studies. Specifically, in our study, maximum RTOG grades 1 and 2 were found in 54.5% and 45.5% of cases on the test side, and 45.5% and 54.5% on the control side, respectively. Notably, toxicity of maximum grades 3 or 4 did not develop at any point during the study. In contrast, as delineated in Table 4, in evaluations of topical treatments such as hyaluronic acid, calendula, trolamine, silver sulfadiazine, and moisturizing barrier cream, the observed rates of maximum RTOG grade 1, 2, 3, and 4 RD were 2–50%, 51–63%, 0–35%, and 0–2%, respectively. Furthermore, in cases involving only general supportive skin care without specific intervention, these rates ranged from 6–58%, 32–63%, 3–53%, and 0–2% for the respective grades [40, 47–52]. In a separate study employing similar radiation parameters and follow-up periods to our research, which evaluated the effects of an EGF-based cream on breast irradiation, maximum grade 3, 2, and 1 RD were observed in 15%, 55%, and 30% of cases, respectively

Table 4 The results of maximum RTOG scores in previous studies

Variable	Biafine (n = 66) [47]	Biafine (n = 25) [48]	Lipiderm (n = 24) [48]	Calendula (n = 126) [40]	Trolamine (n = 128) [40]	MAS065D (n = 22) [49]	Hyaluronic acid (n = 65) [51]	MDBC (n = 157) [52]	Sorbolene (n = 150) [52]
Maximum RTOG Scores									
0	9% (6)			Grade 0–1 59% (74)	Grade 0–1 37% (47)	4.5% (1)	Grade 0–1.5 38.5% (25)	2% (4)	6% (10)
1	50% (33)					86.3% (19)		61% (95)	49% (78)
2	41% (27)			Grade 2–3 41% (52)	Grade 2–3 63% (81)	9% (2)	Grade 2–3 61.5% (40)	35% (55)	43% (70)
3	0% (0)	Grade 3–4 30% (6)	Grade 3–4 59% (10)	0% (0)	0% (0)	0% (0)	0% (0)	2% (3)	2% (3)
4	0% (0)			0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)

Biafine™ (Genmedix Ltd., France): an oil-in-water emulsion with non-steroidal anti-inflammatory properties

Lipiderm™ (G-Pharm Ltd., France): a moisturizing cream commonly used by cosmeticians in Europe and in Israel

Calendula (Pommade au Calendula par Digestion; calendula extract ointment; Boiron Ltd, Levallois-Perret, France)

Trolamine: an oil-in-water emulsion that can enhance skin healing by recruiting macrophages and modifying the concentrations of various immunomodulators

MAS065D (Sinclair Pharmaceuticals Ltd, Godalming, UK): a non-steroidal medical device registered in the US and EU for the symptomatic treatment of RD

(Table 3). More importantly, the results of the quantitative measures of the skin showed that the skin barrier function was maintained on both the test and control sides. The TEWL, whose increase reflect the disruption of the skin barrier function, diminished over time on both the test and control sides, a result that was counter to expectations. Generally, RT is known to impair skin barrier function, leading to an increase in TEWL. Our findings, however, indicate that both creams were effective in maintaining the integrity of the skin barrier function.

Differences in the study design, such as the evaluation scales, and various factors related to RD—including RT dose, RT schedule, use of chemotherapy, smoking, and underlying diseases—may have contributed to the observed discrepancy. In our study, a total dosage of 5050 or 5320 cGy was administered, a figure not significantly different from the radiation doses applied in the previous studies mentioned. Thus, it can be postulated that there are protective effects exhibited by both AdP-containing cream (Easydew MD regen cream) and the control cream without AdP (Easydew MD cream). These protective effects were further corroborated through the biophysical parameters assessed in our study. As detailed in Table 1, both the test and control creams contain various emollients and active ingredients, including ceramide, squalene, cholesterol, vitamin E (tocopherol acetate), hyaluronic acid, and dimethicone [53].

Although our findings demonstrated that both the test and control creams were efficacious in mitigating RD, no statistically significant advantage was observed from the incorporation of AdP. The cream containing AdP was well tolerated, and the skin areas where it was applied exhibited similar toxicities to those observed in the control cream areas without

AdP. Notably, the increase in melanin index following radiation was less pronounced when the test cream with AdP was applied compared to the control cream application. This may be attributed to the melanin synthesis inhibitory effect of AdP [25].

This study is not without limitations. First, it was a preliminary investigation with a restricted sample size, rendering the results inconclusive regarding the efficacy of the AdP-containing cream. Second, we did not consider some potential prognostic factors for RD, such as smoking history, BMI, breast size, or diabetes mellitus. Nevertheless, we endeavored to account for these variabilities that might lead to inherent differences in susceptibility to RD within the treated breast by having each participant utilize both the experimental and control creams. Third, the absence of blinding for both patients and the evaluating clinician could have introduced bias into the results. Finally, with an observation period limited to 8 weeks post-RT initiation, it was not feasible to assess late development or the healing progression of RD subsequent to cream application.

Despite these limitations, the assessment of this novel product for mitigating RD remains valuable. Strategies for mitigating RD must continue to evolve, as numerous cancer patients undergoing RT still struggle with RD. Our professional responsibility demands ongoing exploration of new products, techniques, and innovative methods to minimize or altogether prevent radiation-induced dermatitis.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00520-025-09147-9>.

Author contribution Conceptualization, KYP. and JHC.; methodology, KYP.; software, YGK.; validation, YGK. and KRK.; formal analysis, YGK.; investigation, HSH.; resources, KYP.; data curation,

YGK.; writing—original draft preparation, HSH.; writing—review and editing, HSH. YGK. KRK. JHC. and KYP.; visualization, HSH.; supervision, KYP.; project administration, JHC.; funding acquisition, KYP. All authors have read and agreed to the published version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics statement The patients in this manuscript have given written informed consent to publication of their case details.

Competing interests Kui Young Park has served as an advisor for CGBio Co. Ltd.

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