

Evaluation of topical adjuvant treatment of psoriasis with recombinant epidermal growth factor to control the e-regulation of EGFR: a clinical study

Mahsa Mollapour Sisakht

Tehran University of Medical Sciences

Aida Rezaeinejad

Tehran University of Medical Sciences

Kimia Didehvar

Iran University of Medical Sciences

Yasaman Kiani Doust-Vaghe

Shahid Beheshti University of Medical Sciences

Elham Behrangi

Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Sciences

Azadeh Goodarzi

Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Sciences

Mohammad Ali Nilforoushzadeh

Tehran University of Medical Sciences

Zahra Siahpoosh

KishMediPharm Pharmaceutical Company (KMP. Co)

Mohammad Amir Amirkhani (✉ amirkhani2000@yahoo.com)

Tehran University of Medical Sciences

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Abstract

Deregulation of the epidermal growth factor receptor, which belongs to the ErbB family of receptor tyrosine kinases, is detectable in psoriasis lesions and leads to uncontrolled cell growth, proliferation and differentiation of skin cells. To investigate the effect of epidermal growth factor receptor saturation with a high concentration of epidermal growth factor in a topical cream in the clinical setting in patients with mild to moderate psoriasis, we applied the cream with 5% growth factor in 11 patients and a cream with clobetasol, urea, salicylic acid and Eucerin without growth factor as control on 11 patients in parallel. The therapeutic effect was assessed by blinded clinicians using the Psoriasis Area and Severity Index (PASI) based on severity, erythema, induration and scaling. The result of the clinical trial showed that the PASI index for the standard treatment group was 3.76 ± 1.93 before treatment and 2.9 ± 1.83 after treatment, and for the group receiving EGF was 3.23 ± 2.2 before intervention and 2.52 ± 2.05 after intervention. Although the decrease in PASI was highly significant ($p < .001$) in both the standard and intervention groups before and after the study, individual comparison of each patient before and after treatment showed a significant ($p < .001$) decrease for the intervention group compared with the control group. We conclude that EGF as an adjuvant therapy can effectively control mild to moderate psoriatic lesions without causing side effects. Future clinical trials should be conducted to explore the therapeutic effects.

Highlights

- overexpression of EGFR and the use of inhibitors to control psoriatic lesions is noteworthy
- Safe concentration and high efficacy to saturate the receptors without long-term side effects such as the risk of tumor formation, cumulative release amount of the EGF topical cream was determined
- EGF- topical cream as an adjuvant therapy can effectively control mild to moderate psoriatic lesions

1. Introduction

Epidermal growth factor (EGF), with its 53 amino acid residues, is a powerful protein responsible for the growth, proliferation and differentiation of numerous cell types. This protein binds to the epidermal growth factor receptor (EGFR), which belongs to the ErbB family of receptors and the receptor tyrosine kinase subfamily [1]. Binding can stimulate phosphorylation to activate signaling pathways such as Ras/MAPK, PLC γ /PKC, PI3K/Akt and STAT, which lead to migration, proliferation, cytoprotection and EMT [2]. Figure 1 shows the molecular view and changes during the psoriatic lesion. Many different cancers such as lung, breast, glioblastoma and many others are due to genetic alterations and mutations in EGF levels or EGFR function[3]. In the last decade, numerous studies have described new therapies based on EGFR inhibitors targeting EGF/EGFR, especially for the treatment of skin wounds and cancer [4]. EGF stimulates fibroblasts to increase synthesis of VEGF and HGF as pro-angiogenesis factors and also increases proliferation of keratinocytes and fibroblasts [5]. IGF-1 (via the PI3K pathway) and EGF (through activation of the MAPK pathway) can influence the migration machinery of keratinocytes, which determines the rate of re-epithelialisation and keratinocyte contraction [6]. EGF, which is found in skin

care products, has shown the ability of fibroblasts to produce cytokines [5]. Psoriasis as a chronic skin condition affects 7.5 million adults aged 20 years and older in the United States [7], and the annual US cost of psoriasis was approximately \$112 billion in 2013, meaning that a patient with psoriasis paid \$11,498 for physical symptom relief and emotional health [8]. Moderate to severe psoriasis is usually defined as affecting more than 5 to 10 per cent of the body surface area (BSA) [9], and patients at this stage may receive topical agents as standard treatment: Corticosteroid, Calcipotriol and/or the combination [10]. The main mechanism of psoriasis pathogenesis is still being explored, but can be explained by dysregulation of immunological cell function and keratinocyte proliferation/differentiation [11]. As mentioned above, EGF levels and EGFR activation are related to the differentiation of cells such as keratinocytes (through 3 main mechanisms: reduction of lipid matrix biosynthesis, regulation of crack formation and suppression of tight junction protein expression [12]). Therefore, several researchers link EGF levels to psoriasis symptoms, especially in moderate to severe stages [13–15]. EGF receptors have been shown to be located in the basal cell layer of normal skin, which constantly produces new skin cells. The amount of these receptors is four times higher than in the upper epidermal layer of the skin, while the receptors in the upper epidermal layer in psoriatic lesions are twice as many as in normal skin [15–18]. Several studies demonstrating EGFR overexpression [14] have also shown clinically that the drug can target the receptor, e.g. erlotinib in lung cancer patients[19], lapatinib in renal cancer patients[20], cetuximab in patients with colorectal cancer [21], with remarkable therapeutic effect in patients with chronic psoriasis. In 2003, Yamasaki and et al. demonstrated the mechanism of high-dose epidermal growth factor-dependent cell growth arrest through the autocrine transforming growth factor beta1-ALK5 pathway [22]. Several clinical trials have been conducted to investigate the inhibitory effect of a high dose of EGF to reduce EGFR expression. For example, in 2015 and 2017, the company "Betta 2 pharmaceutical" conducted clinical trials in 136 and 28 patients, respectively, on the effect of 1 icotinib hydrochloride 1.2% as an EGF receptor inhibitor in psoriasis patients [23]. In 2007, a US patent was filed by D. Rudi Neirinckx based on the report of the clinical use of a topical cream containing sulfadiazine and 5 g EGF in two patients with psoriasis, applied twice daily to the affected area for one week. The results after one week showed a significant impression compared to the control group using corticosteroids [18, 24]. Another clinical trial was conducted in 2012 by the pharmaceutical company "Ennar Pharmaceuticals AF" and the University of Zurich on 24 volunteers using EGF topical cream to downregulate EGFR in patients with psoriasis, which is still ongoing [25]. In this study, according to the literature review and in order to determine the inhibitory effect of high-dose EGF in controlling and/or improving the psoriatic lesion, we applied a threshold concentration of EGF as an inhibitory concentration in mild to moderate psoriasis patients compared to the control group receiving standard treatment. The extent of remission and PASI factors were determined by blinded clinicians after 4 weeks. Based on the Food and Drug Administration (FDA) definition of clinical trial phases and given the clinical trials conducted and the patent available using a 5% EGF concentration to inhibit the receptor in the lesion site in the first phase of the clinical trial, we designed this study to assess the efficacy and side effects of the proposed concentration as well as the effectiveness by decreasing psoriasis symptoms compared to a strong standard treatment only by using the saturation (inhibitory effect) of EGFR.

2. Method and materials

2.1. Patient recruitment and setting of the clinical trial

This clinical trial was designed as a simple, randomised, double-blind, single-centre, 4-week, controlled study in parallel groups. All participating patients had to be diagnosed with mild to moderate psoriasis and have at least 5% of body surface area (5-10%) affected. All patients were informed about the study in writing and verbally and signed an informed consent form. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences prior to screening of patients (IRCT20141007019432N8). Patients were enrolled in the dermatology clinic of Hazrat Rasoul Hospital. Patients of either sex aged 18-60 years with mild to moderate active psoriasis covering at least 5% (5-10%) of body surface area (BSA) were eligible. Patients were not eligible if they had received systemic psoriasis treatment in the last 3 months or topical treatment in the last 1 month. Patients with known hypersensitivity or allergy to the EGF-containing product and/or to petrolatum/10% salicylic acid, a history of malignancy, other clinically relevant comorbidities, and participation in another drug trial in the past 30 days were also excluded. 22 eligible patients were randomly assigned to either the treatment or control group (1:1 ratio). Randomisation was done at the beginning of the study by simple randomisation (this method is equivalent to flipping a coin for each subject participating in the study, e.g. heads = active, tails = placebo). The implementation and treatment of the assignments is completely unpredictable). During the 4-week treatment period, patients in the intervention group were treated twice daily for four weeks with a topical cream containing 5% recombinant EGF (SinoBiological, China). The control group received a standard cream containing clobetasol 30 g, urea 15 g and distilled water 15 ccs, salicylic acid 1.5% and Eucerin up to 100 g, without growth factor. Therapeutic effect was assessed by blinded clinicians using the Psoriasis Area and Severity Index (PASI) based on severity, erythema, induration and scaling scores (Fig.2). Clinical photography was also conducted [27]. Efficacy parameters were assessed at baseline and over 4 weeks. Safety was also assessed throughout the study and at the 3-month follow-up. If severe side effects occurred during the study, the study was discontinued.

2.2. Formulation of topical adjuvants:

EGF cream is a water-in-oil (W/O) emulsion formulated according to the USP cold cream formulation [1]. To prepare the oil phase, white wax and wax cetyl ester were first melted in a glass jar on a steam bath with mineral oil (liquid paraffin) and the temperature was raised to 70°C. Then the warm aqueous phase was gradually added together with the melted mixture of borax (sodium borate) and water at the same temperature as the oil phase, stirring continuously until it was blocked. Then wait until the mixture cooled down to about 45°C while stirring. Then the EGF solution was added and homogenised to obtain a uniform and stable cream.

Raw materials	Quantity (g)	Function
Cetyl Esters Wax	125.00	Stiffening agent and Emollient
White wax	120.00	Stiffening agent
Mineral oil	560.00	Emollient, Solvent and vehicles of an oil phase
Sodium borate	5.00	Emulsifying agent
Purified water	178.89	Vehicle and Solvent of an aqueous phase
EGF solution in PBS (pH 7.4) (0.45 mg/ml)	11.11	Active ingredient

Table1. Composition of EGF-containing cream formulations were prepared to a final volume of 1000 g

For the group that was to receive the standard treatment, a formulation of five medicinal components was used under the supervision of a dermatologist according to (Table No. 2). In the first step, the salicylic acid was triturated to a fine, homogeneous powder. Then the fine, homogeneous powder (step 1) was floated with the mineral oil (Light). In the second step, urea was dissolved in a certain amount of distilled water. Then the ingredients of the first and second steps were slowly added to the ointment base with mixing. To achieve a homogeneous dispersion of the ingredients in the ointment, the resulting composition was then continuously mixed under high shear. Finally, the finished product was transferred to the indicated container.

Raw materials	Quantity (g)	Function
0.05% ointment contains clobetasol propionate	300.00	Synthetic corticosteroid, for topical dermatologic use
Urea	150.00	Moisturizer and keratolytics [28]
Salicylic acid powder	15.00	keratolytic compound [29]
Distilled water	150.00	Moisturizer
Eucerin	385.00	Emollient, Ointment Base

Table 2. Composition of topical formulations were prepared as a standard treatment to a final volume of 1000 g

2.3. Release test (In vitro penetration test):

The skin penetration properties of cream containing EGF solution was performed using Franz diffusion cells (PermeGear, Bethlehem, USA). The diffusible area was 1.77 cm² and cellulose acetate with a pore size of 0.45 µm (Sartorius Co., Ltd., Gottingen, Germany) was used as the diffusion membrane. The

receptor compartment was filled with 12 mL phosphate buffer solution (20 mM, pH 6.5), bovine serum albumin 160 µg/ml and 2 mM EDTA and maintained at 37 °C throughout the experiment with a heating circuit. The contents were stirred continuously at 600 rpm. A sample of 360 mg was applied to the donor chamber and in vitro EGF release from the cream formulation was assayed at time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h with 2 ml of sample and the same volume of fresh recipient medium was added to replace the withdrawn samples and maintain sink conditions. Samples were stored at -80°C until analysis. Quantification of EGF in the collected samples was measured using a human EGF ELISA kit (Human EGF Standard ABTS ELISA Development Kit, Peprotech, USA) according to the manufacturer's instructions. The experiments were repeated five times (Fig.3.A).

2.4. Quantification by PASI:

The PASI is a scoring system to assess baseline and response to therapy in psoriasis; the patient's body is divided into four areas: Head (H): 10% of the patient's skin, Arms (A): 20%, Boot (T): 30% and Legs (L): 40%. These areas are assessed individually and then the percentage of affected skin area is converted into a grade from 0 to 6:

- 0% of the affected area
- < 10% of the affected area
- 10-29% of the affected area
- 30-49% of the affected area
- 50-69% of the affected area
- 70-89% of the affected area
- 90-100% of the affected area

For each area, three clinical parameters, namely erythema (redness), induration (thickening) and desquamation (scaling), are assessed by the clinician and the severity is graded on a scale of 0 to 4 (from zero to maximum). The sum of all three severity parameters is then calculated for each skin section, multiplied by the area value for that area and multiplied by the weight of that section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs) [27, 30].

2.5. Statistical analysis:

Statistical analysis was used to compare the results of intervention and control. This analysis was performed using ordinary parametric independent two-way analysis ANOVA with Graph-pad prism software 8.0.2. P-values of < 0.05 were considered statistically significant.

3. Results

The result of the release test of the base cream showed the highest amount of 5 ng/ml from 12 hours to 24 hours, which is indicated as a safe concentration for topical application. The result of the clinical trial

showed that the PASI index for the standard group was 3.76 ± 1.93 before treatment with standard treatment and 2.9 ± 1.83 after treatment, and for the group receiving EGF was 3.23 ± 2.2 before intervention and 2.52 ± 2.05 after intervention. Although the decrease of PASI was highly significant in both standard and intervention groups before and after the study (Fig. 3.C and D), individual comparison of each patient before and after treatment showed a significant decrease for the intervention group compared to the control group (Fig. 3. A and B).

4. Discussion

Psoriasis is a chronic, immune-mediated disease characterized by significantly elevated levels of EGF [14, 31], altered differentiation and hyperproliferation of keratinocytes [14] and a cascade of inflammatory responses, mainly originating from innate immune cells (keratinocytes, dendritic cells, NKT cells, macrophages) and activated T cells and mediated by IFN- γ , IL -1 and tumor necrosis factor- α (TNF- α [31]. On the other hand, many studies dating back to 1986 have shown an upregulation of EGFR and a correlation with psoriasis severity. Wang. S and colleagues described this correlation well in 2019, showing examples of these studies, such as Powell's study showing the inhibitory effect of quinazoline [32], erlotinib, lapatinib, cetuximab and panitumumab, also reported in this article as EGFR inhibitors that resulted in response in psoriatic lesions [14]. Improvement of the psoriatic phenotype in an in vitro setting was also demonstrated by Varani in 2005 using organically cultured skin and inhibiting EGFR tyrosine kinase [33]. A recent in vitro study identified FUT8 (α -(1,6)-fucosyltransferase 8) as a remodeler of EGFR that plays a critical role in the development of the psoriasis phenotype. This study also indicated the presence of an over-activated EGFR in the lesional epidermis of a psoriasis-like mouse and human model, although knockout of FUT8 in a IL -23 psoriasis-like mouse model resulted in a lower level of EGFR activation and improvement in disease phenotype [34]. Another study has shown that DcR3 (Decoy receptor 3 (DcR3) is a soluble receptor of Fas ligand (FasL)) can be detected in the epidermal layers of psoriasis skin lesions. In this study, increased levels of DcR3 and down-regulated FasL were detected in the serum of psoriasis patients. EGFR signaling plays a central role in modulating DcR3 expression in keratinocytes. In addition, inflammatory cytokines, particularly TNF- α , can induce DcR3 expression in keratinocytes, which in turn may contribute to the progression of psoriatic skin lesions [35]. Given this information, the overexpression of EGFR and the use of inhibitors to control psoriatic lesions is noteworthy. However, in tumor-derived cell lines overexpressing EGFR, growth inhibition and an inhibitory effect on tumor cells were observed in response to a high dose of EGF [36, 37], which is similar to the mechanism of down-regulation of FSH and LH secretion by saturation of GnRH receptors in response to a constant GnRH level [18]. On the other hand, the accumulated data on the safety assessment of topical application of growth factors is controversial. A study of EGF, TGF α and suramin as GFs inhibitors on mouse skin for 9 days showed that the alteration of the skin active phosphocreatine (PCR)/creatin kinase (CPK) system depends on skin pathology, this system regenerates adenosine triphosphate energy reserves during ischaemia [38]. Another preliminary in vitro evaluation suggests that cosmetic topical products containing growth factors as active ingredients can be considered safe and effective [39] without promoting the proliferation of abnormal cells. Considering various studies elucidating the role of

GFs, especially EGF, in cancer metastasis [40, 41], the use of safe dosage of GFs and, more importantly, the provision of sufficient amount of GFs is crucial. According to our own research, the release test of the base cream resulted in the highest amount of 5 ng/ml, which is indicated as a safe concentration for topical application. It should be noted that the release amount is lower than we expected due to the lack of extraction and digestion of the cream. In designing the experiment, we tried to perform the release test under conditions very similar to the site of application at the donor site. The use of drug delivery systems, such as encapsulated GFs within a polymer network [42] or nano-liposomes [43], aid penetration and sustained release. When EGF or other GFs are sparingly administered, such as topical application, it is possible that they diffuse away from the wound bed, resulting in a reduction in the local concentration of administered GFs. This may result in large amounts of GFs being administered and the need to continuously repeat treatment, potentially leading to an increased risk of tumor formation and cell proliferation [42]. To achieve an acceptable safety profile and high efficacy to saturate the receptors without long-term side effects such as the risk of tumor formation, we used a 5% V/V EGF cream for psoriasis patients based on international regulatory requirements [44]. The cumulative release amount of the EGF cream showed a release of approximately 5ng/ml over 2 to 24 hours. As the procedure was repeated twice daily, the patient received at least 10ng/ml of EGF per day into the psoriasis lesion, which can be considered a safe dose. On the other hand, previous research has shown that psoriasis lesions rarely progress to skin cancer, which is due to the function of the CCHCR1 gene (Coiled-Coil α -Helical Rod protein 1, HCR), which acts as a negative regulator of proliferation [45]. Topical application of 5 g EGF/gramme and sulphadiazine to two psoriasis cases twice daily for one week showed significant improvement compared to treatment with corticosteroids [18]. Our clinical outcome also showed a highly significant difference PASI before and after treatment with EGF cream compared to standard treatment. In addition, previous studies above-mentioned EGFR inhibitors have shown that skin toxicity is caused by the expression of chemokines such as CCL2, CCL5, CCL27 and CXCL14 and the blunt production of barrier antimicrobial proteins [46]. Early inflammation caused by dendritic cells, macrophages, granulocytes, mast cells, and T cells was shown in 2003 after the use of EGFR inhibitors [47], (Fig. 1) the effect that must not occur when EGF is used as a receptor inhibitor. However, the comparison of PASI before and after treatment for individuals showed a significantly lower amount in the treatment group compared to the standard treatment. This may suggest that although EGF saturates the receptor at the site of the lesion to control the symptom in a similar way to standard treatment, this mechanism for controlling severity, especially in mild psoriasis patients, does not show skin toxicity, either at 1 month or at 3 months of follow-up.

5. Conclusion and future direction

This was a clinical feasibility study on the safety of the new therapeutic agent EGF, which is used at an acceptable concentration as a recombinant growth factor to control skin lesions in psoriasis patients as an adjuvant therapy and may help patients achieve a better quality of life and healing satisfaction. The clinical data showed that EGF cream containing 5% of bare growth factor can control patients' symptoms as well as the standard treatment, which contains clobetasol, urea, salicylic acid and Eucerin. The result

of this study shows that topical application of EGF without any adjuvant is safe and can help doctors manage the severity of the disease. The next step of the study is a comprehensive randomised, multicentre clinical trial to treat patients with psoriasis.

Declarations

Ethics approval and consent to participate: Regulatory monitoring was conducted by the independent group of Tehran University of Medical Sciences. All investigators completed a human investigation protocol approved by TUMS. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences prior to screening of patients (IRCT20141007019432N8).

Consent for publication:

The authors affirm that human research participants provided informed consent for publication of the images in Figure 2.

Availability of data and materials:

Raw data were generated at skin and stem cell research center, TUMS. Derived data supporting the findings of this study are available from the corresponding author [MA Amirkhani] on request.

Competing interests:

The authors declare no conflict of interest, financial or otherwise.

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Authors' contributions:

Conception and design of study: Mahsa Mollapour Sisakht and Mohammad Amir Amirkhani. Acquisition of data: Aida Rezaeinejad, Kimia Didehvar, Yasaman Kiani Doust-Vaghe, Zahra Siahpooshand Mahsa Mollapour Sisakht. Analysis and/or interpretation of data: Mahsa Mollapour Sisakht, Mohammad Ali Nilforoushzadeh, Mohammad Amir Amirkhani. Formulation: Yasaman Kiani Doust-Vaghe. Patient selection and relevant data interpretation: Elham Behrangi, Azadeh Goodarzi. Patient follow-up: Mahsa Mollapour Sisakht, Aida Rezaeinejad, Kimia Didehvar. Drafting the manuscript: Aida Rezaeinejad, Kimia Didehvar, Yasaman Kiani Doust-Vaghe and Mahsa Mollapour Sisakht. Revising the manuscript critically for important intellectual content: Mahsa Mollapour Sisakht and Mohammad Amir Amirkhani

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Data Availability Statement (Required):

Raw data were generated at skin and stem cell research center, TUMS. Derived data supporting the findings of this study are available from the corresponding author [MA Amirkhani] on request.

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Figures

to the activation, proliferation and production of antimicrobial peptides (e.g. LL -37 cathelicidin and β -defensins), chemokines (e.g. CXCL1, CXCL9 to CXCL11 and CCL20) and S100 proteins (e.g. S100A7-9) by keratinocytes. CCL19 produced by macrophages led to an accumulation of T cells and dendritic cells. On the other hand, upon binding of a ligand to the EGFR, two important intracellular signaling pathways are activated by the EGFR: the RAS-RAF-MEK-MAPK signaling pathway, which controls gene transcription, cell cycle progression from G1 phase to S phase and cell proliferation, and the PI3K-Akt signaling pathway, which activates a cascade of anti-apoptotic and pro-survival signaling. Feedback loops involving keratinocytes, fibroblasts and endothelial cells contribute to tissue reorganization by activating endothelial cells, proliferating and depositing extracellular matrix. Neutrophils in the epidermis are attracted by chemokines, including interleukin-8 (CXCL8) and CXCL1 [26]. EGF epidermal growth factor, KGF-1/2 keratinocyte growth factor types 1 and 2, and TGF- β transforming growth factor β , MAPK mitogen-activated protein kinase, P phosphate, PI3K phosphatidylinositol 3,4,5-kinase.

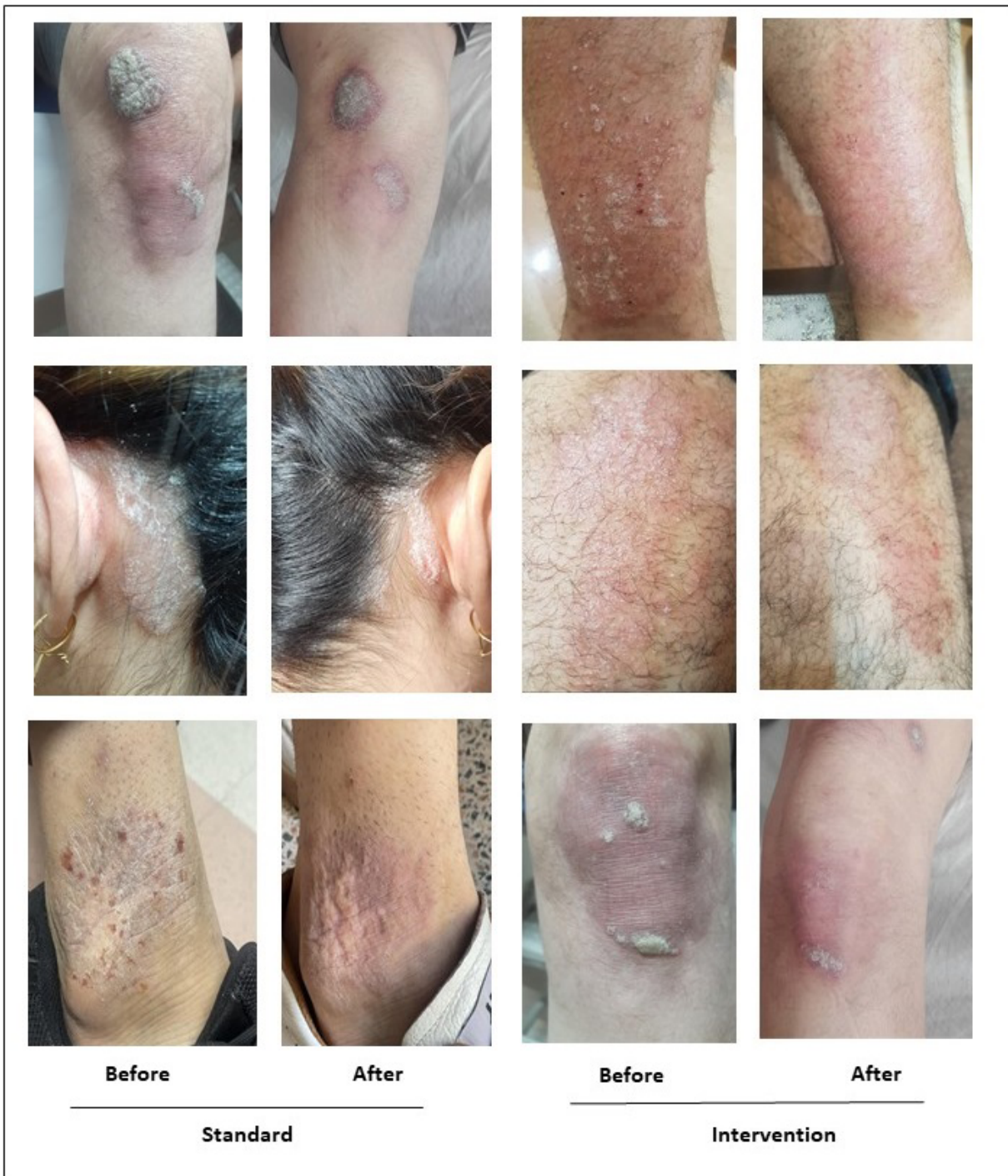


Figure 2

Patients before and after treatment in the control group and in the intervention group. During the 4-week treatment period, patients in the intervention group were treated twice daily for four weeks with a topical cream containing 5% recombinant EGF. The control group received a standard cream containing clobetasol 30 g, urea 15 g and distilled water 15 ccs, salicylic acid 1.5% and Eucerin up to 100 g, without growth factor.

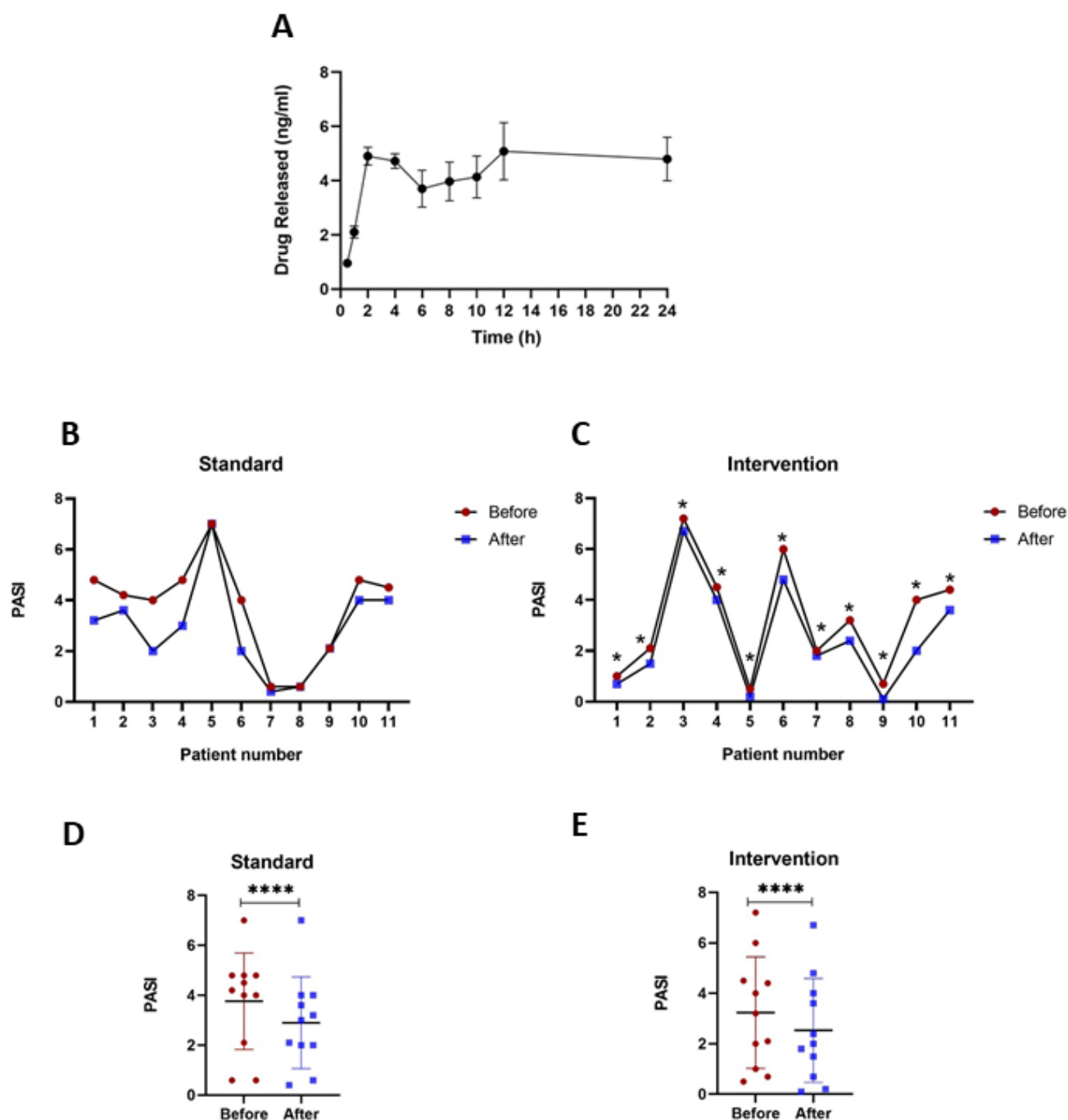


Figure 3

Therapeutic effect was assessed by blinded clinicians using the Psoriasis Area and Severity Index (PASI) based on severity, erythema, induration and desquamation. A. The skin penetration properties of the EGF-containing cream were studied using Franz diffusion cells. B. C. Statistical analysis of PASI was performed for each group (control and intervention) before and after treatment with standard treatment and EGF cream. D. E. Cumulative data from each group together (intervention VS standard treatment)

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