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ORIGINAL ARTICLE

Topical doxycycline foam 4% for prophylactic management of epidermal growth factor receptor inhibitor skin toxicity: an exploratory phase 2, randomized, double-blind clinical study

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Abstract

Purpose Acneiform rash, a common toxicity of epidermal growth factor receptor inhibitors (EGFRIs), can cause patient discomfort, warranting changes in treatment. This study investigated the safety, tolerability, and efficacy of a novel doxycycline foam, FDX104 4%, for managing EGFRI-related skin toxicity.

Methods This was an exploratory phase 2, randomized, double-blind, placebo-controlled study. Subjects had metastatic colorectal cancer and were being treated with either cetuximab or panitumumab plus chemotherapy. Treatment (twice-daily topical FDX104 4% on one side of the face and vehicle foam on the other for 5 weeks) was initiated 7 ± 3 days prior to EGFRI therapy. Rash severity, safety, and tolerability were evaluated at 2 and 4 weeks after EGFRI start.

Results The mean maximal rash grade was lower with FDX104 4% vs vehicle, and fewer subjects developed moderate-to-severe (grades 2–3) rash. On the Global Severity Score scale, a statistically significant difference favored FDX104 4% over vehicle ($P = .047$). Adverse events (AEs) ($n = 68$) occurred in 20 subjects; most were mild or moderate. The most common AEs were oral mucositis, nausea, and vomiting, common to chemotherapy and EGFRI treatment. Study-drug–related AEs were experienced by five subjects and consisted of mild, local skin reactions. No study-drug–related systemic side effects were reported.

Conclusion Twice-daily, topical administration of FDX104 4% as an adjunct to either cetuximab or panitumumab was safe and well tolerated, and appeared to prevent the onset of rash, especially severe rash.

ClinicalTrials.gov identifier Trial Registration NCT02239731

Keywords Epidermal growth factor inhibitor · Acneiform rash · Skin toxicity · Colorectal cancer · Topical doxycycline foam · FDX104

Introduction

Epidermal growth factor receptor inhibitors (EGFRIs) are widely used targeted agents that have been approved for the treatment of various tumor types [1]. Cetuximab and panitumumab, monoclonal antibodies that target the extracellular ligand-binding domain of the EGF receptor, are commonly used in the treatment of advanced colorectal and head and neck cancers [1–3].

While EGFRIs are essential cancer treatment options, various dermatologic adverse events (AEs) commonly develop, including maculopapular and papulopustular rash, commonly referred to as acne-like rash (or folliculitis), xerosis, fissures, telangiectasia, hyperpigmentation, and hair and nail changes

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[2–4]. In some clinical studies with EGFRIs, particularly cetuximab and panitumumab, the incidence of rash is reportedly as high as 95% (with grades 3 or 4 rash in 18% of subjects) [2, 3]. EGFRI-associated dermatologic toxicities can have a profound impact on a patient's quality of life, daily activities, independence, and psychological and emotional well-being [5]. Consequently, adherence to therapy could be compromised [2–4]. With significant dermatologic toxicity, dose reduction or even interruption of EGFRI therapy is often required [2, 3].

The management of rash in EGFRI-treated patients is thus a key step in maintaining them on treatment and also avoiding further treatment-related disability. The most common interventions to prevent or manage the onset of rash include antibiotics, corticosteroids, and antihistamines, according to a recent systematic review of published recommendations of rash management strategies [6]. Topical antibiotics or corticosteroids are usually recommended for mild rash, whereas their oral formulations, plus the strategy of delaying or reducing EGFRI therapy, are recommended for more severe rashes [6]. Doxycycline, minocycline, and tetracycline are the main antibiotics recommended for the management of EGFRI-induced rash [7, 8]. Recent guidelines recommend both prophylactic use as well as the concomitant use of appropriate medication throughout EGFRI treatment to effectively manage rash [7, 8]. Although prophylactic antibiotic treatment is supported by clinical studies, not all guidelines have adopted this approach in their recommendations, and further clinical evidence is required [6, 7, 9, 10]. When oral antibiotics are used, their efficacy in managing EGFRI-induced dermatologic toxicities can be offset by their associated systemic side effects [11].

To provide patients with a potentially more tolerable medication for rash, a novel topical foam formulation of doxycycline hyclate 4%, FDX104 4%, was developed. This clinical study aimed to investigate the use of FDX104 4%, as compared with foam vehicle, as a prophylactic therapy against skin toxicity in subjects treated with EGFRI therapies.

Methods

Study design and plan

This was an exploratory phase 2, randomized, double-blind, multicenter, vehicle-controlled study investigating the safety, tolerability, and efficacy of a topical doxycycline foam, FDX104 4%, for managing EGFRI-induced skin toxicity in subjects with advanced colorectal cancer who were receiving cetuximab or panitumumab in combination with chemotherapy. The study was conducted at four oncology centers in Israel.

In this study, each subject acted as his or her own control by treating one side of the face with FDX104 4% and the other side with the matching foam vehicle serving as topical placebo. FDX104 4% or foam vehicle was applied topically to the same respective side of the face twice daily, once in the morning and once in the early evening. Treatment was initiated at 7 ± 3 days prior to EGFRI treatment start and was continued for a total of 5 weeks. Efficacy and safety evaluations and assessments were performed at 2 and 4 weeks after initiation of EGFRI therapy (i.e., 3 and 5 weeks post-FDX104 4% treatment). At the end of FDX104 4% treatment, subjects were followed up for an additional 4 weeks.

The study protocol was approved by the independent ethics committees, and signed informed consent was obtained for each subject.

Subject population

Eligible for enrollment were male or nonpregnant, nonlactating female subjects, age ≥ 18 years, with any cancer and receiving cetuximab or panitumumab on a weekly or 2-weekly basis. Eligible subjects had not received any prior EGFRI treatment within 3 months of study start.

Subjects were excluded from the study if any of the following were present: (1) prior allergic reaction or severe intolerance to doxycycline and/or tetracycline; (2) use of systemic antibiotics within 7 days prior to treatment start, or other topical treatments (e.g., topical antibiotics) within 14 days prior to treatment start; and (3) any other skin conditions or clinical findings that might confound the evaluation of rash, make topical application of FDX104 4% unacceptable, or place the subject at undue risk.

Safety and efficacy assessments

The primary objective was the safety and tolerability of FDX104 4%, assessed by the evaluation of the incidence and severity of AEs, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), as well as vital signs.

The efficacy of FDX104 4% in preventing facial skin toxicity was also assessed in the following exploratory objectives: (1) mean maximal rash grade, (2) incidence of maximal skin rash, and (3) time to first severe rash. Two grading scales were used to assess rash severity: (1) the Global Severity Score (GSS) scale (also known as the Generalized Rash Scale), adapted from Scope A, et al., [12] which provides a visual scale of rash severity (Supplemental Fig. 1), and (2) the modified MASCC (Multinational Association of Supportive Care in Cancer) EGFRI Skin Toxicity Tool (MESTT) scale, which uses the number of papules and pustules designated for the whole face for each half of the face (Supplemental Table 1) [13].

Rash severity was assessed in two ways: (1) real-time assessment at each subject visit by a blinded investigator using the MESTT scale and (2) central assessment by a blinded independent dermatologist at the end of the study using the GSS scale (based on blinded review of photographs taken at study visits). Subjects were photographed at each study visit using a uniform digital imaging system to ensure repeatable images between time points.

Statistical analyses

AE data were summarized as numbers and percentages. Vital signs data were summarized by ranges, medians, means, and standard deviations (SDs). For exploratory efficacy objectives, categorical variables were compared and analyzed by the chi-square test or by the Fisher-Irwin exact test, while continuous variables were calculated by mean, median, and SD. Tests for normality were done by the Shapiro-Wilk normality test. Results between pairs of continuous variables were analyzed by the Wilcoxon paired signed-rank test. The study population was small, and thus the study was not powered to detect statistical significance in treatment effects.

Results

Baseline subject characteristics and disposition

A total of 24 subjects were randomized and received at least one dose of FDX104 4%; 20 subjects completed the study (2 subjects had protocol violations, 1 withdrew consent, and 1 was withdrawn by the investigator due to use of systemic antibiotics, a prohibited medication) (Supplemental Fig. 2). All subjects were Caucasian; mean age was 55.2 years (range, 24.9–78.0), and 62.5% were males. All subjects had advanced colon cancer, with a mean disease duration of 17.9 months (range, 1–96 months) and were to receive either cetuximab or panitumumab on a weekly or biweekly basis in combination with chemotherapy (FOLFOX/FOLFIRI/capecitabine). Most subjects (83.3%) had received prior chemotherapy for cancer. At baseline, only one subject was recorded to have a mild rash, based on GSS, and no subject had a history of dermatologic conditions (other than acne at childhood) (Table 1). The overall subject adherence rate to study treatment was 97.5% (mean) or 100% (median).

Table 1 Baseline subject characteristics

Characteristic ($N = 24$)	
Mean age (range), year	55.2 (24.9–78.0)
Gender, *n* (%)	
Male	15 (62.5)
Female	9 (37.5)
Caucasian, *n* (%)	24 (100)
Ethnicity, *n* (%)	
Arab	3 (12.5)
Ashkenazi	9 (37.5)
Sepharady	10 (41.7)
Mixed	2 (8.3)
Cancer type, *n* (%)	
Colon	24 (100)
Treatment, *n* (%)	
Cetuximab	12 (50)
Panitumumab	11 (49)[a]
Concomitant chemotherapy (FOLFIRI/FOLFOX/capecitabine)	23 (95.8)
Previous cancer treatments, *n* (%)	
Chemotherapy	20 (83.3)
Surgery	17 (70.8)
Other biological treatment	8 (33.3)
Irradiation	4 (16.7)
Prior EGFRI	4 (16.7)

[a] One subject included in the intent-to-treat population, who was randomized to FDX104 4%, withdrew from the study before receiving the EGFRI treatment due to use of a prohibited medication (systemic antibiotic)

EGFRI epidermal growth factor receptor inhibitor

Efficacy evaluation

Overall, 79% of the subjects developed rash, and 58% developed moderate-to-severe rash on at least one side of their face within 4 weeks of EGFRI treatment initiation, which is consistent with the known incidence of EGFRI-associated rash [4, 10].

Based on the GSS scale, on the FDX104 4%–treated sides, moderate-to-severe rash and severe rash developed in 9 (37.5%) and 4 subjects (16.7%), respectively, as compared with 13 (54.2%) and 9 (37.5%) subjects for the vehicle-treated side ($P = .063$). For the MESTT scale, 15 (62.5%) subjects developed moderate-to-severe rash on the FDX104 4%–treated side, as compared with 16 (66.7%) subjects for the vehicle-treated side ($P = .344$) (Table 2).

Mean maximal rash grade was numerically lower on the FDX104 4%-treated side than on the vehicle-treated side in all subjects, based on both GSS (1.3 vs 1.7; $P = .063$) and MESTT (1.6 vs 1.9; $P = .344$) scales (Fig. 1). Similar observations were reported for subjects who had developed moderate-to-severe rash on at least one side of the face. For the MESTT scale, the reduction of rash severity from 1.9 on the vehicle-treated side to 1.6 on the FDX104 4%-treated side represents an effect size of 15%, which is a positive signal.

A method of ranking based on clinical significance was used, where a 2-grade difference between the two treatment sides in the same subject was considered more clinically significant than a difference of a 1-grade change. Included in this

Table 2 Incidence of rash after 4 weeks of EGFRI therapy

Rash severity (grade)	*N* = 24 (ITT analysis)	
	FDX104 4% *n* (%)	Vehicle *n* (%)
GSS scale		
No rash (0)	5 (20.8)	5 (20.8)
Mild (1)	10 (41.7)	6 (25.0)
Moderate (2)	5 (20.8)	4 (16.7)
Severe (3)	4 (16.7)	9 (37.5)
P value (Wilcoxon signed-rank)	0.063	
MESTT scale		
No rash (0)	6 (25.0)	5 (20.8)
Mild (1)	3 (12.5)	3 (12.5)
Moderate (2)	9 (37.5)	6 (25.0)
Severe (3)	6 (25.0)	10 (41.7)
P value (Wilcoxon signed-rank)	0.344	

GSS generalized rash scale, *ITT* intent-to-treat, *MESTT* modified Multinational Association of Supportive Care in Cancer EGFRI Skin Toxicity Tool

analysis were the 14 subjects who had moderate-to-severe rash on at least one side of the face. Based on the GSS scale, clinical response (improvement of ≥ 1 grade) was achieved in six subjects (42.9%) on the FDX104 4%-treated side vs 1 subject (7.1%) on the vehicle-treated side (Table 3). In 7 subjects (50%), there was no difference in rash severity between FDX104 4% vs vehicle. Analysis of the paired differences revealed a statistically significant difference in favor of FDX104 4% over vehicle ($P = .047$).

We observed a lower probability for the vehicle-treated side to remain free of severe rash over time, indicating a shorter time to development of a severe rash with the vehicle. However, this difference did not reach statistical significance (HR = 0.2; $P = .096$) (Supplemental Fig. 3). A difference in the occurrence of rash between treatment sides could be observed as soon as 2 weeks (Fig. 2a, b) or 3 weeks (Fig. 2c) after EGFRI initiation.

Safety evaluation

Overall, 20 subjects (83.3%) experienced an AE; however, most of these AEs were mild (76.5%) or moderate (17.6%) (Table 4). The most common AEs were oral mucositis (29.2%), nausea (20.8%), vomiting (20.8%), and pruritus (16.7%), which are commonly known to be related to EGFRI or chemotherapy treatment [4, 5]. Only one serious AE was recorded, febrile neutropenia, which was considered unrelated to the study drug treatment. In total, six study-related AEs were reported in five subjects; they were mild, local dermal skin reactions, and all, except for pruritus and dryness around the mouth and nose, resolved by study completion. There were no study drug-related systemic AEs. No subject was discontinued from the study drug due to AEs.

Discussion

Dermatologic toxicity can be a dose-limiting AE of EGFRI treatment. Doxycycline, currently only available in oral formulation, is one of the main antibiotics recommended for managing EGFRI-induced rash; however, it has been associated with various systemic side effects, affecting the gastrointestinal system, (e.g., nausea, vomiting, diarrhea), nervous system (e.g., dizziness), and respiratory system (e.g., rhinitis) [7, 9, 11].

Prophylactic treatment with tetracyclines to manage EGFRI-induced skin toxicity has been recommended by recent guidelines [8]. In addition, a recent systematic review and meta-analysis of 13 studies including more than 1000 patients showed that prophylaxis with oral tetracycline can significantly reduce the incidence and severity of cutaneous acneiform rash [14].

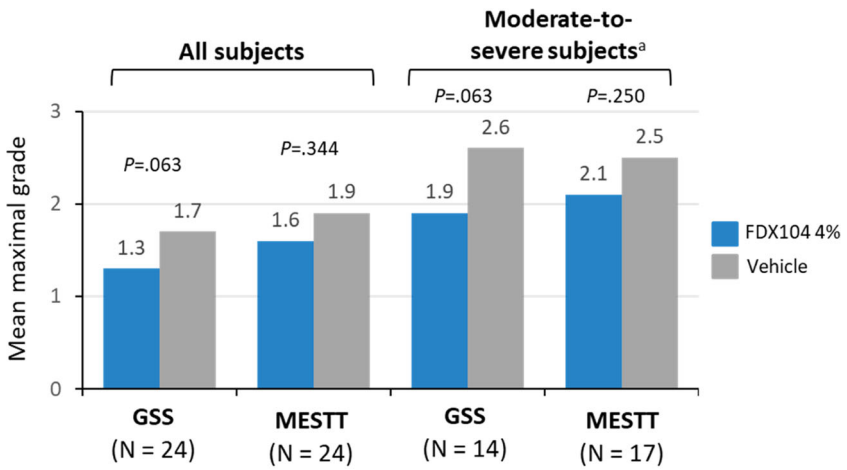

Fig. 1 Mean maximal rash grades after 4 weeks of EGFRI therapy (ITT analysis). EGFRI epidermal growth factor receptor inhibitor, GSS Global Severity Scale, ITT intent to treat, MESST MASCC (Multinational Association of Supportive Care in Cancer) EGFRI Skin Toxicity Tool

[a]These subjects had developed moderate-to-severe rash on at least one side of the face.

Table 3 Rash grade on FDX104 4%- and vehicle-treated sides, and the delta between them (response population)

Score (GSS)	No rash ($n = 5$)					Mild rash ($n = 5$)					Moderate or severe rash ($n = 14$)													
FDX104 4%	0	0	0	0	0	1	1	1	1	1	2	1	1	3	3	2	1	1	2	1	2	2	3	3
Vehicle foam	0	0	0	0	0	1	1	1	1	1	2	3	3	3	3	2	2	3	1	3	3	2	3	3
Score difference	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	1	2	−1	2	1	0	0	0

GSS Global Severity Score

In our study, FDX104 4%, a novel topical formulation of doxycycline, was investigated as a twice-daily, prophylactic treatment, to prevent skin toxicity in subjects receiving cetuximab or panitumumab. Overall, numerically fewer subjects developed moderate-to-severe rash on the FDX104 4%-treated side than on the vehicle-treated side, and the mean maximal rash grade was numerically lower for FDX104 4% than for its vehicle. FDX104 4% appeared to prevent rash in subjects receiving EGFRI therapy, particularly for the population who developed moderate-to-severe rash on either side of the face. More subjects achieved clinical response (improvement of ≥ 1 grade) on the FDX104 4%-treated side than on the vehicle-treated side; paired rank difference was statistically significant ($P = .047$). Subject adherence to using FDX104 4% was very high throughout the study, yielding a mean adherence rate of 97%. In clinical practice, as high as 70% of patients will require an EGFRI dose reduction because of EGFRI-induced skin toxicity, and about 35% will discontinue treatment [15]. Therefore, the results of this study may have meaningful implications not only for patients' quality of life during EGFRI treatment but also for primary cancer treatment.

FDX104 4% appeared to be well tolerated and was not associated with any drug-related systemic side effects. No subjects discontinued the study due to AEs. The majority of AEs experienced by subjects were mild or moderate. The most common AEs were oral mucositis, nausea and vomiting, and pruritus, unrelated to the study drug treatment. The six study-drug–related AEs reported were mild, local dermal reactions, and four resolved before the end of the study. No severe drug-related AEs were reported.

Although the NCI-CTCAE is commonly used by oncologists to rate rash severity, the criteria are broad in nature and may not adequately capture the essence of EGFRI-associated toxicity. Our study used two established rating scales. The GSS is a predefined qualitative visual scale developed by Scope and colleagues to assess the severity of cetuximab-related acneiform facial rash [12]. The modified MESTT scale was developed by the MASCC Skin Toxicity Study Group to evaluate the side effects of EGFRI treatment [13]. This scale was modified for use in assessing EGFRI-induced rash severity by applying the severity descriptors intended for the whole face to just half the face. This was done in order to have a higher discrimination of the more severe rashes. Both grading scales in this study showed either a statistically significant difference or a positive trend favoring FDX104 4% over vehicle in the onset and severity of EGFRI-associate rash.

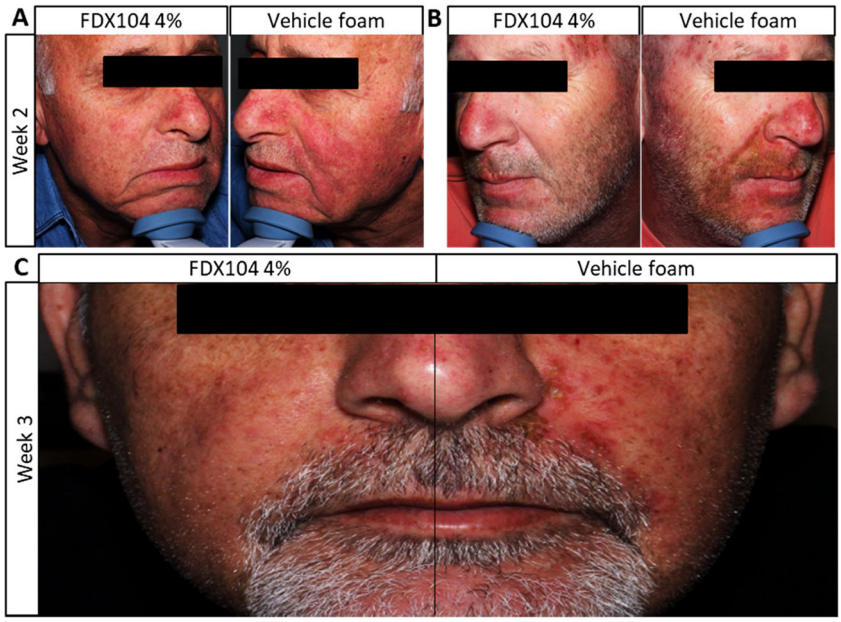

Fig. 2 Representative images of rash at week 2 (**a**, **b**) or week 3 (**c**) from EGFRI initiation. EGFRI epidermal growth factor receptor inhibitor

Table 4 Overall summary of safety profile

	(*N* = 24)
Subjects with any AE, *n* (%)	20 (83.3)
Subjects with SAE, *n* (%)	1 (4.2)
Subjects with severe AE, *n* (%)	3 (12.5)
Most common AEs (≥ 2% subjects), *n* (%)	
Oral mucositis	7 (29.2)
Nausea	5 (20.8)
Vomiting	5 (20.8)
Pruritus	4 (16.7)
Diarrhea	3 (12.5)
Dry skin	3 (12.5)
Constipation	2 (8.3)
Stomach pain	2 (8.3)
Fatigue	2 (8.3)
Fever	2 (8.3)
Myalgia	2 (8.3)
Peripheral sensory neuropathy	2 (8.3)
Cough	2 (8.3)
Febrile neutropenia	2 (8.3)
Subjects with treatment-related AE[a] *n* (%)	5 (20.8)
Pruritus[a]	2 (8.3)
Skin hypopigmentation	1 (4.2)
Dryness around mouth and nose	1 (4.2)
Erythema of face after application of foam	1 (4.2)
Facial pain	1 (4.2)

[a] One pruritus AE event had a weak relationship to study drug

AE adverse event, *SAE* serious adverse event

An important limitation of the study was the small number of subjects enrolled, which precluded it being powered to detect a statistically significant treatment effects. The within-subject study design allowed for a higher power for assessing the efficacy variables. Nevertheless, it involves two potential subject-related limitations: unintentional mixing up of the treatments and bias in applying the treatment (i.e., applying the treatment that showed better efficacy on one side of the face to both sides). To minimize these possibilities and limit the observed differences between treatment groups (sides of the face), canisters were clearly marked, and measurements of adherence were strictly monitored. The adherence rate in this study was very high, at > 97%.

Overall, this phase 2, randomized, double-blind, exploratory clinical study showed that FDX104 4%, a novel topical foam formulation of doxycycline hyclate, 4%, was well tolerated, and demonstrated potential rash-preventative effects in subjects receiving EGFRI therapy. The findings support further evaluation of FDX104 4% in larger clinical trials.

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Compliance with ethical standards

Conflict of interest This study was supported by Foamix Pharmaceuticals. Einat Shacham Shmueli served as principal investigator on this study and has received a grant from Foamix Pharmaceuticals. Ravit Geva, Nirit Yarom, and Ayala Hubert served as investigators on this study. Rita Keynan, Tal Hetzroni Kedem, Dov Tarmakin, and Mitchell Shirvan are employees of Foamix Pharmaceuticals. Meir Eini serves as a consultant for Foamix Pharmaceuticals. Mitchell Shirvan, Tal Hetzroni, and Meir Eini receive stock options from Foamix Pharmaceuticals. Ravit Geva reports other from MSD, Novartis, BMS, Roche, Janssen, Takeda, Medison, Merck, and Pfizer, outside the submitted work. The authors state that they have full control of all primary data, and they agree to allow the journal to review their data if requested.

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