

MEASURING THE PREDICTIVE VALUE OF SEROLOGICAL QUANTIFICATION OF CYTOKINES WITH THE ONSET OF INFLUENZA-LIKE SIGNS AND SYMPTOMS INDUCED BY IMIQUIMOD 3.75% CREAM: RESULTS OF A SINGLE CENTER, OPEN-LABEL, PROOF OF CONCEPT TRIAL

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INTRODUCTION

- Imiquimod is an immune response modifier that is FDA approved for the treatment of actinic keratosis (AKs), external genital warts, and superficial basal cell carcinoma.¹
- Imiquimod is a potent inducer of interferon (IFN)- α and other pro-inflammatory cytokines.²
- Some patients treated with topical imiquimod develop influenza-like symptoms (e.g., myalgia, malaise, headache, low-grade fever, and fatigue) that may be related to elevated levels of pro-inflammatory cytokines associated with application of the drug.³
- This study was carried out to assess correlations between influenza-like symptoms and cytokine levels in patients who applied imiquimod cream to their skin for 14 days. Other variables that might influence emergence and severity of symptoms, including age, severity of local skin reactions, the amount of surface area involved, and the area of the body exposed were also evaluated.

METHODS

Design

- Single-center open-label study.

Subjects

- 22 men and women with 5-20 AKs between 30 and 89 years of age.

Treatment

- The designated treatment area (entire face or balding scalp; or chest or upper extremities) was cleansed with an approved cleanser and allowed to dry for 5 minutes prior to application of imiquimod 3.75% cream to a total area of 200 cm². The treatment period was 14 days.

Endpoints

- Clearance of AKs.
- Frequency of symptoms indicative of an influenza-like response, including, fever, headache, fatigue, malaise, gastrointestinal symptoms, dizziness, myalgia, and arthralgia.
- Change from baseline at subsequent study visits (days 8, 15, 43, and 57 [end of study]) in:
 - Cytokines – interleukin (IL) -6, IL-8, IL-12, IL-13, IL-2 receptor (R), tumor necrosis factor- α (TNF), IFN- α , and IFN- γ
 - Frequency of local skin reactions of erythema, scabbing/crusting, edema, erosion/ulceration, exudate, flaking/scaling/dryness and pruritus.

RESULTS

Subjects

- Characteristics of subjects enrolled and areas treated are summarized in Table 1.

Clearance of AKs

- All but one subject experienced either complete clearance or partial clearance of actinic keratoses with no more than 3 remaining in the treatment field.

Table 1. Subject characteristics

Characteristic	N=22
Age (years)	
Mean (standard deviation)	62.8 (8.99)
Median	59
Age group, n (%)	
≥ 30 years to ≤ 59 years	12 (54.5)
≥ 60 years to ≤ 89 years	10 (45.5)
Sex, n (%)	
Female	7 (31.8)
Male	15 (68.2)
Area of Treatment n (%)	
Entire Face or Balding Scalp	11 (50.0%)
Chest or Upper Extremities	11 (50.0%)

Frequency of Influenza-like Symptoms

- Systemic symptoms characteristic of influenza occurred infrequently during the treatment period (Table 2).

Table 2. Influenza-like symptoms that emerged during treatment

Symptom	Occurrence During Treatment (n)
Fever	1
Myalgia	1
Fatigue	0
Malaise	1
Headache	4
Gastrointestinal symptoms	3
Dizziness	3
Arthralgia	3

Relationship Between Clearance of AKs and Influenza-like Symptoms

- There was no apparent relationship between clearance on the occurrence of symptoms (Table 3).

Table 3. AK clearance in subjects with and without influenza-like symptoms

Systemic Symptoms during treatment	Baseline AK count, mean (median)	End of treatment AK count, mean (median)
Yes	14.0 (14.0)	2.9 (0.0)
No	13.7 (14.0)	2.4 (1.0)

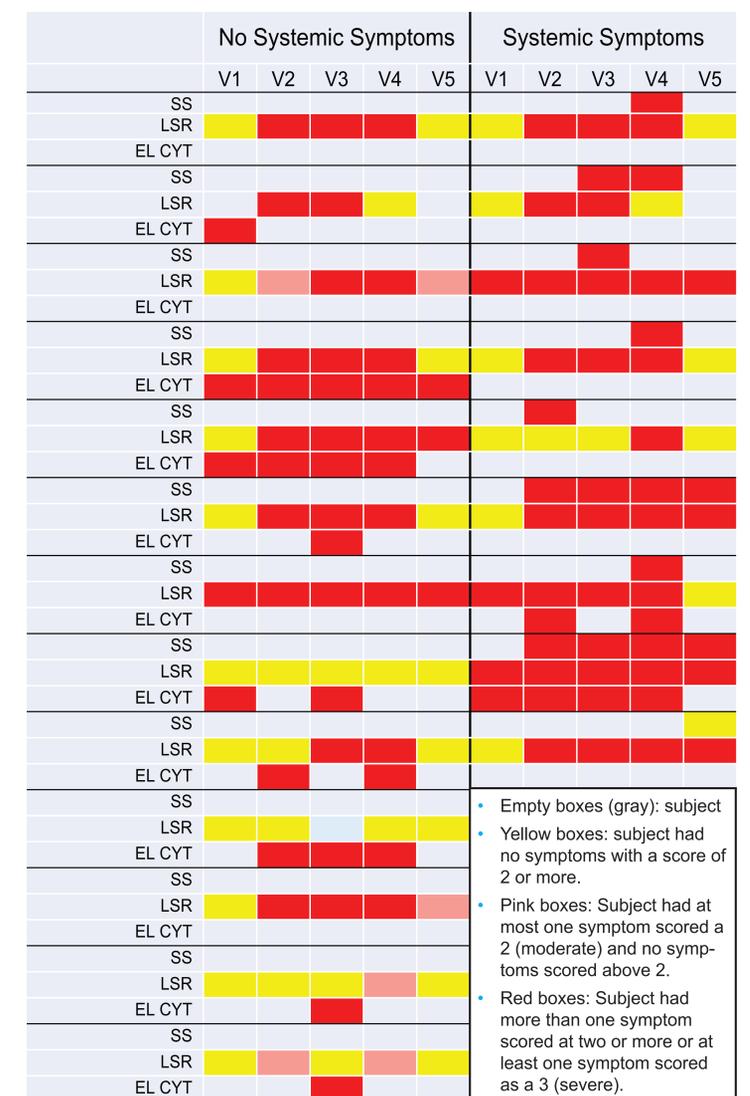
Changes from Baseline in Cytokine Levels

- Twelve subjects had elevations in at least one cytokine at one or more post-baseline visits (Table 4).
- There were no apparent relationships between the occurrences of cytokine elevations and either the occurrence of influenza-like symptoms or local skin reactions (Figure 1).

Table 4. Cytokine elevations during treatment.

Subject	Visit 1	Visit 2	Visit 3	Visit 4
4	IL-2	IL-2	IL-2, IL-13	IL-2, IL-2R, IL-13
7			IL-13	IL-13
8	IFN- γ	IFN- γ	IFN- γ	IFN- γ
10		IL-2, IL-12	IL-2	IL-2, IL-12, IFN- γ
11	IL-6, IL-2R, IL-13	IL-6, IL-2R, IL-13	IL-6, IL-2R, IL-13	
12			IL-13	
13	IL-13		IL-13	
15			IL-8, IL-13	
18	IL-13			
20		IL-13		IL-13
21	IL-13	IL-12		
23		IL-8	IL-13	IL-13

Figure 1. Temporal relationships among systemic symptoms (SS), local skin reactions (LSR) and elevations in cytokines (EL CYT) for patients with and without SS.



CONCLUSION

- Treatment on the face led to more incidence of flu like symptoms in younger patients
- Elevations in pro-inflammatory cytokines did not appear to predict the development of either systemic symptoms or local skin reactions.
- Elderly patients treated on the body were less likely to develop reactions of the four groups.

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