Effectiveness and satisfaction with imiquimod for the treatment of superficial basal cell carcinoma in daily dermatological practice

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Abstract
Background The use of imiquimod for the treatment of superficial basal cell carcinoma (sBCC) in actual conditions of the daily practice has been poorly studied.
Objective A prospective, observational and multicentre study was designed to gather information on the effectiveness and safety of imiquimod therapy in patients with sBCC in daily practice. Patient’s satisfaction with imiquimod was also assessed.
Methods A total of 370 adult patients with sBCC were included in the study. Patients were treated with imiquimod 5% cream five times per week for 6 weeks. A maximum of three lesions per patient were treated. Patients were requested to complete diary cards to register treatment-related events and had a final visit within 16 weeks after the end of treatment.
Results Target sBCCs included 471 tumours, with a mean (SD) 1.3 (0.6) lesions per patient. Most sBCC were primary tumours (92.6%). Tumours were clinically diagnosed in 63.2% of cases and histologically confirmed in 36.8%. Previous sBCC had occurred in 42% of the patients. The mean number of daily applications of imiquimod was 1.0 (0.1) for a mean of 4.9 (0.5) days per week. The mean duration of treatment was 6.0 (1.0) weeks. In 13 patients (14 target sBCCs), rest periods were indicated with a mean of 5.0 (2.8) rest days. The clearance rate was 83.2%. Clearance rate was independent of the tumour size. Local skin reactions (mostly erythema) occurred in 85% of cases (mild 37%, moderate 39% and severe 24%). Nine patients discontinued imiquimod treatment because of severity of application site reactions. Most patients (82.1%) were very satisfied or satisfied with imiquimod.
Conclusions The present data from a prospective study carried out in a community setting adds evidence of the usefulness and favourable clinical profile of imiquimod 5% cream when administered for treating sBCC.

Introduction
Basal cell carcinoma (BCC) is the most common skin cancer in fair skinned populations and the incidence of BCC continues to rise by approximately 10% per year.1 Although mortality is low, this malignancy causes considerable morbidity and places a huge burden on healthcare services worldwide.2 Superficial BCC (sBCC) comprises up to 25% of all histological subtypes and appears as erythematosus, slightly scaly and well-defined patches mostly found on the trunk and limbs. In highly sun-exposed populations, lesions are also common on the face.3

There are a variety of treatment options for BCC, including surgery and different destructive procedures, photodynamic therapy and other non-invasive modalities, such as topical 5-fluorouracil and the immune-response modifier imiquimod. Imiquimod

1See Appendix.
available as a 5% cream is approved in different countries for use in sBCC using a regimen of once daily, five times per week for 6 weeks. Imiquimod acts as a Toll-like receptor (TLR)-7 agonist stimulating the dendritic cells in the epidermis and dermis to release interferon α and other cytokines. It is thought to exert its anti-tumour effect via modification of the innate and cell-mediated immune response pathway with activity against tumour cells resulting in apoptosis.4,5

Data from clinical trials with imiquimod 5% cream for the treatment of sBCC have shown encouraging results with short-term clearance rates (clinical and histological) in the range between 73% and 90%.6–15 In two identical randomized, double-blind vehicle-controlled phase III studies, subjects with one sBCC were dosed with imiquimod or vehicle cream once daily 5 or 7 times per week for 6 weeks. The difference in clearance rates between the two imiquimod dosing groups was not statistically significant and according to these results, the five times per week regimen was recommended.19 On the other hand, in large phase III studies the histological clearance rates have been consistently found to be higher than the clinically observed clearance rate.9,10 In a 5-year long-term follow-up study carried out in Europe, the estimate of overall treatment success for all treated patients at the end of follow-up was 78% (81% if histological data were considered).16 Application site reactions, which are the most common adverse effects, are seen in up to 87% of patients treated for sBCCs with imiquimod applied five times per week for 6 weeks.17 The most common local site reactions are erythema, oedema, induration, erosion, scaling, crusting, pruritus and burning sensations. In some patients, the severity of application site reaction warrants transient discontinuation of treatment. Rest periods, however, do not affect the efficacy of treatment.

Imiquimod trials and several published clinical series provide evidence of the benefits of imiquimod therapy for sBCC. However, there is limited data on the use of imiquimod 5% cream in routine daily practice. To our knowledge, no previous study carried out in a community setting in a large sample of patients with sBCC treated with imiquimod has been reported. Therefore, a nationwide prospective multicentre study was conducted with two aims: (i) to assess the effectiveness, safety and tolerability of treatment with imiquimod 5% cream for sBCC in conditions of daily practice, and (ii) to determine patient’s satisfaction with topical imiquimod application.

Methods

Study design

A prospective, observational and multicentre study was designed to assess the effectiveness, safety and tolerability of imiquimod 5% cream for the treatment of patients with sBCC in conditions of daily dermatological practice. Secondary objectives of the study were the assessment of the patient’s satisfaction with topical imiquimod and compliance with treatment as well as to assess whether dermatologists prescribed imiquimod in accordance with the product technical specifications. The study was carried out at the outpatient clinics of the services of dermatology of different hospitals throughout Spain in the routine clinical setting. The participating centres belonged to the public Spanish National Health Care System. A total of 92 dermatologists from 32 hospitals agreed to participate voluntarily in the study. Ten patients per site had to be enrolled over a 3-month period.

The study protocol was approved by the ethics committee of the participating centres and the local agencies of the Autonomous Communities. All patients were fully informed about the characteristics of treatment with imiquimod 5% cream and gave written informed consent.

Patients

Between 1st January 2006 and 31st March 2007, all consecutive patients of both sexes aged 18 years or older, with histologically proven sBCC or lesions clinically consistent with sBCC in which treatment with imiquimod 5% cream was indicated by the dermatologist in charge according to the product technical specifications were eligible, provided that they gave written informed consent and were able to understand and follow the study procedures. Patients with other subtypes of BCC were excluded as were those in whom the use of imiquimod was contraindicated according to the product technical specifications. Pregnant women and nursing mothers were also excluded.

Study procedures and data collection

The study was based on a first (baseline) visit, a variable number of follow-up visits during and after treatment with topical imiquimod scheduled by the participating dermatologist according to his/her practice, and a final visit at 3 months to assess the effectiveness of treatment within a maximum interval of 16 weeks after the end of treatment. Baseline and final visits were mandatory by study protocol. The baseline visit was the initiation of treatment with imiquimod 5% cream (12.5 mg imiquimod in monodose sachets of 250 mg cream) (Aldara™, 3M España, Madrid, Spain). The recommended dosing frequency was once daily five times per week (5 times per week) for 6 weeks prior to normal sleeping hours. The cream was to remain on the skin for at least 8 h without occlusion, and then removed with mild soap and water. Dermatologists could prescribe treatment-free rest periods at their own decision. A maximum of three sBCCs per patient were selected for treatment.

At the first visit the following variables were recorded: demographics, underlying chronic diseases and use of concomitant medications, previous sBCC (site and treatment), and characteristics of the target lesion(s), such as site and diagnostic method, site, size, primary or recurrent sBCC, previous treatment, and date of starting imiquimod. Patients were given a diary card, one per sBCC to be treated, to register all days in which imiquimod was applied, missed doses and rest days (according to the prescribed regimen or as a result of local site reactions). Clinical evolution of lesions, local
skin reactions and their treatment, rest periods, adverse events (AEs) and compliance with treatment were recorded in the follow-up visits. At the final visit, effectiveness of imiquimod 5% cream and patient’s satisfaction with treatment were also evaluated.

For each lesion, effectiveness of treatment was assessed in terms of presence or absence of clearance defined according to clinical or histological criteria used in the routine clinical practice by the participating dermatologist. Biopsy was only carried out if this procedure was indicated according to the standard clinical practice of each centre. A 7-point Likert scale was used to assess patient’s satisfaction, which included the following categories: extremely satisfied, satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, dissatisfied and extremely dissatisfied. Safety was assessed by recording the AEs observed by the investigator or reported by the patient either spontaneously or answering to open questions. Details on the seriousness, severity, action taken, outcome and relationship to imiquimod treatment were also recorded. With regard to tolerability, frequency and severity of local skin reactions were evaluated. Compliance with treatment was assessed by checking diary cards.

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) (version 15.0) for Windows was used for the analysis of data. Double data entry was carried out with a subsequent validation to guarantee the quality and consistency of the data. Continuous variables are expressed as mean and standard deviation (SD) and qualitative variables are described as frequencies and percentages. The chi-squared test or the Fisher’s exact tests were used for the comparison of categorical variables and the Student’s t-test for continuous variables. Statistical significance was set at \( P < 0.05 \).

**Results**

A total of 373 eligible patients were recruited but three patients were excluded (the diagnosis of sBCC was not confirmed in two and missing baseline data in one patient). Twenty-one patients discontinued the study, 18 during the treatment period and three during the post-treatment period. Subject disposition during the study is shown in Fig. 1.

The study population included 370 patients, 200 men and 170 women, with a mean (SD) age of 68.4 (13.2) years. The total number of sBCCs was 471, with a mean of 1.3 (0.6) target lesions per patient. Target sBCCs were diagnosed clinically in 63.2% of cases and histologically confirmed in 36.8%. Most sBCCs were primary tumours (92.6%), recurrent tumours occurred in 35 (7.4%) cases. Tumours were located on the face in 34.8% of cases, in the trunk in 29.3% and in the extremities in 24.2%. Concomitant malignancy or immunosuppressive disorders were present in 34 (9.2%) patients. History of previous sBCC was recorded in 154 (41.6%) patients, 14 of which had been treated with imiquimod. The baseline characteristics of patients and site of target tumours are shown in Table 1. The mean (SD) size of target sBCC was 1.6 (2.9) cm².

### Table 1 Baseline characteristics and location of target superficial basal cell carcinoma (sBCC)

<table>
<thead>
<tr>
<th>Data</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>370</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>200</td>
</tr>
<tr>
<td>Female</td>
<td>170</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>68.4 (13.2)</td>
</tr>
<tr>
<td>Concurrent malignancy or immunosuppressive disorder</td>
<td>34 (9.2)</td>
</tr>
<tr>
<td>History of previous sBCC</td>
<td>154 (41.6)</td>
</tr>
<tr>
<td>Treatment of previous sBCC</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>124 (80.5)</td>
</tr>
<tr>
<td>Electrocoagulation</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Curettage</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>5-FU</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>14 (9.1)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Target tumours</td>
<td>471</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>164 (34.8)</td>
</tr>
<tr>
<td>Ear and external auditory canal</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Neck and scalp</td>
<td>41 (8.7)</td>
</tr>
<tr>
<td>Trunk</td>
<td>138 (29.3)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>92 (19.5)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>22 (4.7)</td>
</tr>
<tr>
<td>Not specified</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Size, cm², mean (SD)</td>
<td>1.6 (2.9)</td>
</tr>
</tbody>
</table>

sBCC, superficial basal cell carcinoma.

The mean number of daily applications of imiquimod 5% cream was 1.0 (0.1) for a mean of 4.9 (0.5) days per week. The mean duration of treatment was 6.0 (1.0) weeks. Deviations from
the product technical specifications in the number of applications per week were recorded in 39 sBCCs and in the number of treatment weeks in 90. In 13 patients (14 target sBCCs), rest periods were indicated by the dermatologist in charge, with a mean of 5.0 (2.8) rest days. The mean number of follow-up visits including the final visit was 2.9 (0.8).

A total 446 target tumours from 346 patients were evaluable at the final visit. The clearance rate was 83.2% (371/446). In the large majority of lesions, the final outcome was defined clinically, with a clinical clearance rate of 94.9% (352/371). In only 19 cases, biopsies were also performed to confirm histological clearance. The clearance rate was similar in primary tumours (83.1%) than in recurrent lesions (83.9%) \( (P = 0.92) \). On the other hand, clearance rate was independent of the tumour size. Although tumours in which clearance was obtained showed a lower size \( [\text{mean } 1.5 \text{ (2.6)} \text{ cm}^2] \) than those in which clearance was not obtained \( [\text{mean } 1.9 \text{ (4.1)} \text{ cm}^2] \), differences were not statistically significant \( (P = 0.20) \). Clearance rates were higher in tumours \( \leq 2 \text{ cm}^2 \) than in larger tumours \( (>2 \text{ cm}^2) \) but differences were not significant (Fig. 2).

As shown in Table 2, clearance rates were higher in tumours located on the face \( (84\%) \) than in tumours located on the ear and external auditory canal \( (72.7\%) \) or the lower extremities \( (72.7\%) \) but statistically significant differences according to site were not observed \( (P = 0.70) \). In addition, clearance rates were also similar in patients without malignancy or immunosuppressive disease \( (84.3\%) \) than in those with malignancy or immunosuppressive disorder \( (73.8\%) \) \( (P = 0.13) \).

During the treatment period, AEs (excluding local reactions) were reported by four patients, with an incidence of 1.1%. Adverse events included headache in two patients, influenza-like symptoms in one, and irritative dermatitis in one. The intensity of AEs was mild in three patients and moderate in one but no patient discontinued imiquimod treatment because of an AE.

Table 2. Erythema, crusting, oedema, erosion and scaling were the frequency and intensity of local site reactions are shown in Table 3. Erythema, crusting, oedema, erosion and scaling were the most common application site reactions. Local infection was suspected in 15 cases \( (4.2\%) \), 11 of which were treated with fusidic acid. Post-treatment hypopigmentation was observed in 22% of cases. Nine patients discontinued imiquimod during the treatment period because of severity of local site reactions. There were no significant differences in the percentage of local site reactions between target tumours with or without rest periods \( (100\% \text{ vs. } 93.5\%) \) \( (P = 0.8) \). However, the occurrence of severe reactions was significantly higher in the group of lesions with rest periods \( (50\%) \) than in those without rest periods \( (28.1\%) \) \( (P = 0.03) \). Given that rest periods were mostly indicated in patients with more (or more severe) local site reaction. Treatment for application site reactions was prescribed in 30.2% of cases and included topical antibiotics in 46.7%, corticosteroids in 20.6%, combined corticosteroids and antibiotics in 21.5% and antiseptics in 13.1%.

Most patients \( (82.1\%) \) were extremely satisfied or satisfied with imiquimod therapy; only 4.3% of patients manifested to be dissatisfied or extremely dissatisfied (Fig. 3).
At the final visit, diary cards were collected in 206 cases (46.2%). Compliance with treatment was very high, with application of topical imiquimod for a mean of 31.1 (16.7) days and 7.7 (9.3) days off. The mean number of missed doses was 0.3 (0.8) days. Compliance >80% with imiquimod regimen was observed in 99% of the patients.

**Discussion**

The therapeutic potential of imiquimod in clinical practice has been recognized for the past decade. Following an approved indication for the treatment of external genital warts, imiquimod 5% topical cream has received further approval for treating actinic keratosis and small sBCC in adults. Currently, imiquimod 5% topical cream is a widely studied and characterized TLR-7 agonist available in the clinical milieus.18,19 The present prospective and multicentre study carried out in a large sample of patients with sBCC provides data on the effectiveness and safety of imiquimod topical therapy in real life conditions. To our knowledge, no previous prospective study in a large sample of patients with sBCC treated with imiquimod in actual conditions of the daily practice has been reported. Therefore, this study adds descriptive information on the use of this immune response modulator in patients seeking medical care at dermatological clinics in Spain. The present findings may be useful to gather postapproval safety and efficacy data.

In this clinical series of 370 patients, with a total of 471 target sBCCs treated with imiquimod 5% cream, a clearance rate of 83.2% was obtained. In the majority of patients, the final outcome was defined clinically only (clinical clearance rate of 94.9%), histologically in 3.2% of cases and clinically and histologically in 1.9% of cases. The high clearance rate confirms the efficacy of imiquimod for treating sBCC reported in clinical trials.6,8,9,14,16,20 The fact that the final outcome was histologically defined in only 19 patients supports the dermatologist’s ability to clinically determine that the tumour is gone at the end of treatment and that clinical clearance is ultimately used in clinical practice. On the other hand, the low rate of histological confirmation is related to the naturalistic design of the study. Because the study was carried out in daily practice conditions, no indications regarding histological assessment of the final outcome were predefined, which is different than strict requirements imposed in phase III clinical trials. Moreover, in accordance with the objective of the study to assess how dermatologist used imiquimod 5% cream for sBCC in their routine practices, there were no restrictions regarding excluding patients with recurrent lesions or concomitant malignancies or immune-suppression. All patients were visited at 3 months but visits at 6 and 12 months were not scheduled because assessment of recurrences was not the purpose of the study. However, there is a need for continued follow-up of these patients as recurrences can occur later than 3 months post-treatment. On the other hand, our findings of a similar clearance rate for primary and recurrent tumours may be related to the small number of recurrent lesions in this study.

On the other hand, the present findings support the effectiveness of topical imiquimod in sBCC located on the face. In contrast to target tumour locations in clinical trials predominating in the trunk and extremities,9,10 the face was the most common site in our study followed by the trunk and extremities. In this respect, the effectiveness of imiquimod was unrelated to size and location of lesions.

Application site reactions occurred in a high percentage of cases (85%) but the intensity was mild or moderate in most of them. These consisted largely of erythema followed by erosion, crusting and oedema, and in general were managed adequately with rest periods. The fact that rest periods were only indicated in 3.3% of the tumours (with a mean of five rest days) is a further indicator of the mild intensity of local site reactions. However, in nine (2.4%) patients, local skin reactions were severe enough to cause discontinuation. In a pooled analysis of two phase III, randomized, vehicle-controlled studies,9,10 4% of subjects in the imiquimod five times per week group discontinued because of an AE or local site reaction. In this study, it was observed that the proportion of subjects experiencing application site reactions during the treatment period was significantly higher in the seven times per week imiquimod group compared with the five times per week group.9 In this study, the five times per week dosing regimen was used. Moreover, deviations from the product technical specifications in the number of applications per week were recorded in only 8.3% of cases (39/471 target sBCC). This finding is clinically relevant and confirms the correct prescription of imiquimod.

Despite the fact that the high prevalence of application site reactions noted in daily practice conditions, the degree of patient’s satisfaction with imiquimod was very high (82% of patients were very satisfied or satisfied), which may be explained by the high clearance rate and the mild intensity of local skin reactions. In two studies evaluating the use of imiquimod for the treatment of external genital warts, patient’s satisfaction was 86.5% and 89.1% respectively.21,22 Patient’s satisfaction with the use of topical imiquimod in sBCC has not been addressed in previous studies.

In our study, a compliance of more than 80% with imiquimod regimen was found in 99% of the patients. This high compliance rate should be interpreted with caution, taking into account that
diary cards were only collected for 46% of the target tumours. However, no previous data on compliance with imiquimod therapy in patients with sBCC in routine daily practice have been reported.

In summary, the present data from a prospective, observational and multicentre study carried out in daily practice conditions adds evidence for the usefulness and favourable clinical profile of imiquimod 5% cream when used for the treatment of sBCC.

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References


Appendix

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