Treatment of Bowen’s Disease with Ingenol Mebutate: A Retrospective Study

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Abstract: Management of BD is widely variable and there is little evidence for the most appropriate treatment. Our aim was to evaluate the effectiveness of ingenol mebutate (IM) gel in the treatment of patients with Bowen’s disease (BD). We performed a retrospective analysis of 24 cases of biopsy-confirmed BD treated with IM. Data retrieved from the patients’ file included age, sex, anatomic sites, clinical images of lesions, histopathological data of skin biopsies, local skin reactions, clinical and histological response to treatment, alternative treatments tried and follow-up. The majority of patients were females (18/24, 75%), with an average age of 79.5 years (range 53-90 years). Four of the 24 patients were lost to follow-up. The average duration of follow-up was 10.4 months (range 0.5-44 months). After treatment with IM, 41.7% of patients showed complete clinical resolution. Retreatment with IM of six non-responder patients led to three more cases of successful healing. Therefore, 54.2% of patients with BD lesions achieved complete resolution after treatment with one or two cycles of IM. Local skin reactions were mostly mild or moderate, and only 12.5% were regarded as severe. The results indicate that topical IM gel may be considered as a safe and beneficial non-invasive treatment option for BD, especially in patients who are poor candidates for surgery and anatomical sites that are unsuitable for other treatments. The acceptable safety profile, short treating course and easy self-application of IM gel may improve patient compliance.

Keywords: Bowen’s Disease, Ingenol Mebutate, Dermatopathology, in situ Squamous Cell Carcinoma

1. Introduction

Bowen’s disease (BD) is a form of in situ squamous cell carcinoma, which may develop to invasive skin malignancy in 3 to 5% of cases if left untreated [1, 2]. Etiological factors of BD include irradiation -mainly ultraviolet radiation-, carcinogens, immunosuppression, viral and some others like chronic injury or dermatoses, being long-term sun exposure the strongest risk factor for the development of the disease [3, 4]. BD affects predominantly older individuals, with a higher risk of comorbidities, and is frequently located on body sites with poor wound healing.

There are multiple treatment options for BD and many variables that may influence the choice of treatment in an individual, including age and immunological status of the patient, number and size of lesions, and sites affected [5]. Although there is no single modality that can be regarded as optimum for BD management, a non-invasive procedure is often the most convenient therapeutic approach. Nonsurgical treatments such as topical therapies (i.e., 5-fluorouracil and imiquimod) and photodynamic therapy (PDT), cryotherapy and radiotherapy, among others, are viable alternatives to surgical excision [4].

Topical ingenol mebutate (IM) gel, an agent made from the plant Euphorbia peplus that has been approved for a field-directed treatment of actinic keratosis, has recently also been used to treat BD patients. However, only few cases and one clinical study have reported on its therapeutic efficacy in the treatment of BD. In the present study we aimed to report the results of a retrospective study of 24 patients with BD treated with IM gel.
2. Methods

Data from 24 patients with biopsy-confirmed BD were collected between October 2014 and May 2018, in two hospitals in Barcelona, Spain. The following data were retrieved from the patients’ file: age, sex, anatomic sites, clinical images of lesions, histopathological data of skin biopsies (pre and post-treatment), local skin reactions, clinical response to treatment, alternative treatments tried and follow-up.

Lesions on the head were treated with 0.015% IM gel applied once daily for three consecutive days, and lesions on the trunk and extremities were treated with 0.05% IM gel applied once daily for two consecutive days.

Clinical resolution was evaluated at 3 months after treatment by clinical and histological (skin biopsy) assessments. Outcomes were classified as either complete resolution (CR) or non-complete resolution (NCR; including partial or non-existent response to treatment). Patients who experienced NCR of lesions were subsequently treated with IM under the same regimen as outlined previously, topical 5% imiquimod (five times a week for 6 weeks), topical PDT with methyl aminolevulinate (MAL-PDT) (2 sessions separated by a one-week interval), or excisional surgery, depending on the physician’s criteria.

Local skin reactions were rated as mild, moderate, or severe.

Follow-up time was from the 3-month post-treatment clinical assessment to the last clinical visit.

3. Results

Clinical characteristics of patients included in the study and clinical response to the treatment of BD are shown in Table 1. The study population included 18 females (75%) and 6 males (25%) with an average age of 79.5 years (range 53-90 years). Most lesions were located on the trunk and extremities (14/24, 58.3%). Four of the 24 patients (19, 20, 22 and 23) were lost to follow-up.

| Patient No. | Clinical characteristics of patients with Bowen’s disease and response to ingenol mebutate treatment. |
|-------------|------------------------------------------------------------------------------------------------------|
|             | Patient No. | Age (years) | Sex (F/M) | Anatomic sites | Local reaction | Clinical resolution (CR/NCR) | 1st Alternative therapy |
| 1           | 80          | F           | pretibial  | moderate      | CR            | NA                        |
| 2           | 73          | F           | thigh      | mild          | CR            | NA                        |
| 3           | 87          | F           | preauricular | mild      | NCR           | IM                        |
| 4           | 87          | F           | mandibular | mild          | CR            | NA                        |
| 5           | 84          | M           | scalp      | severe        | NCR           | Surgery                   |
| 6           | 90          | F           | cheek      | moderate      | NCR           | IM                        |
| 7           | 67          | F           | pretibial  | mild          | NCR           | Imiquimod 5%               |
| 8           | 83          | F           | cheek      | moderate      | CR            | NA                        |
| 9           | 81          | F           | temple     | moderate      | NCR           | IM                        |
| 10          | 74          | M           | lower leg  | mild          | NCR           | IM                        |
| 11          | 53          | F           | forehead   | severe        | NCR           | MAL-PDT                   |
| 12          | 88          | F           | cheek      | moderate      | CR            | NA                        |
| 13          | 78          | M           | thigh      | mild          | NCR           | MAL-PDT                   |
| 14          | 86          | F           | chest      | mild          | CR            | NA                        |
| 15          | 80          | F           | thigh      | moderate      | CR            | NA                        |
| 16          | 77          | F           | lower leg  | severe        | CR            | NA                        |
| 17          | 78          | F           | lower leg  | mild          | CR            | NA                        |
| 18          | 88          | F           | chest      | mild          | NCR           | Surgery                   |
| 19          | 88          | F           | lower leg  | mild          | NCR           | IM                        |
| 20          | 77          | M           | finger     | mild          | NCR           | IM                        |
| 21          | 77          | F           | lower leg  | moderate      | NCR           | Imiquimod 5%               |
| 22          | 88          | F           | lower leg  | mild          | NCR           | MAL-PDT                   |
| 23          | 76          | M           | lower leg  | mild          | NCR           | NA                        |
| 24          | 68          | M           | lower leg  | moderate      | CR            | NA                        |

| Patient No. | Clinical resolution (CR/NCR) | 2nd Alternative therapy | Clinical resolution (CR/NCR) | No. of treatments | Follow-up (months) |
|-------------|-----------------------------|------------------------|-----------------------------|-------------------|-------------------|
| 1           | NA                          | NA                     | NA                          | 1                 | 44                |
| 2           | NA                          | NA                     | NA                          | 1                 | 23                |
| 3           | CR                          | NA                     | NA                          | 2                 | 13                |
| 4           | NA                          | NA                     | NA                          | 1                 | 29                |
| 5           | NCR                         | Imiquimod 5%           | CR                          | 3                 | 6                 |
| 6           | CR                          | NA                     | NA                          | 2                 | 24                |
| 7           | NCR                         | Imiquimod 5%           | CR                          | 3                 | 3                 |
| 8           | NA                          | NA                     | NA                          | 1                 | 26                |
| 9           | CR                          | NA                     | NA                          | 2                 | 6                 |
| 10          | NCR                         | Surgery                | CR                          | 3                 | 0.5               |
| 11          | NCR                         | Surgery                | CR                          | 3                 | 0.5               |
| 12          | NA                          | NA                     | NA                          | 1                 | 11                |
| 13          | NCR                         | Surgery                | CR                          | 3                 | 2                 |
performing a second alternative treatment with 5% imiquimod. Lesions were completely resolved. Follow-up: 10.4 months, range 0.5-44 months), 20 of 24 alternative therapies after NCR with IM, showed complete case reports suggest that IM is a potentially effective and safe approach is to use non-invasive topical therapies and reserve other treatments for recurrent/refractory cases. Several recent studies support these findings.

Regarding non-complete responder patients after IM treatment (14/24, 58.3%), 42.9% (6/14) were treated with IM gel as a first alternative therapy, 21.4% (3/14) with PDT, 14.3% (2/14) with 5% imiquimod, and 14.3% (2/14) underwent surgery; one patient was lost to follow-up (patient 23).

Among patients who were treated with a second cycle of IM gel (42.9%; 6/14) as a first alternative treatment, three of them (3/6, 50%) achieved complete resolution of lesions, and the other three cases (3/6, 50%) were subjected to a third treatment: one patient underwent surgery and resolved clinically; the other two were treated with MAL-PDT but failed to respond (patients 19 and 20; lost to follow-up). Overall, 54.2% of patients (13/24) were successfully cured after one (10/13, 76.9%) or two cycles (3/13, 23.1%) of IM.

Patients treated with PDT (3/14, 21.4%) as a first alternative therapy after NCR with IM, failed to respond favorably. One patient was lost to follow-up (patient 22), and the other two achieved clinical resolution after surgery.

Finally, one patient treated with 5% imiquimod (1/2, 50%) and one patient treated with surgery (1/2, 50%) as first alternative therapies after NCR with IM, showed complete healing. Non-resolved lesions were successfully cured after performing a second alternative treatment with 5% imiquimod.

At the end of the follow-up period (average duration of follow-up: 10.4 months, range 0.5-44 months), 20 of 24 lesions were completely resolved.

### 4. Discussion

The treatment of BD is widely variable, and at present there is little evidence for the most appropriate regimen [6]. BD mainly affects the elderly and the usual treatment approach is to use non-invasive topical therapies and reserve other treatments for recurrent/refractory cases. Several recent case reports suggest that IM is a potentially effective and safe treatment option for BD, with a short treating course [7-12]. However, only one study evaluating the effectiveness of IM gel in the treatment of BD has been published until now [13].

CR: complete resolution; NCR: non-complete resolution; NA: not applicable

| Patient No. | Clinical resolution (CR/NCR) | 2nd Alternative therapy | Clinical resolution (CR/NCR) | No. of treatments | Follow-up (months) |
|-------------|-------------------------------|-------------------------|-----------------------------|------------------|-------------------|
| 14          | NA                            | NA                      | NA                          | 1                | 0.5               |
| 15          | NA                            | NA                      | NA                          | 1                | 0.5               |
| 16          | NA                            | NA                      | NA                          | 1                | 0.5               |
| 17          | NA                            | NA                      | NA                          | 1                | 0.5               |
| 18          | CR                             | NA                      | NA                          | 2                | 4                 |
| 19          | NCR                            | MAL-PDT                 | NCR                         | 3                | follow-up loss    |
| 20          | NCR                            | MAL-PDT                 | NCR                         | 3                | follow-up loss    |
| 21          | CR                             | NA                      | NA                          | 2                | 6                 |
| 22          | NA                            | NA                      | NA                          | 2                | follow-up loss    |
| 23          | NA                            | NA                      | NA                          | 1                | follow-up loss    |
| 24          | NA                            | NA                      | NA                          | 1                | 0.5               |

After treatment with IM, 41.7% of patients (10/24) showed complete clinical resolution, and the rest (14/24, 58.3%) showed non-complete resolution of lesions. Clinical outcomes after treatment did not depend on the anatomic site affected. In terms of safety, local skin reactions were mostly mild (13/24, 54.2%) or moderate (8/24, 33.3%), and only 12.5% were regarded as severe.

Regarding non-complete responder patients after IM treatment (14/24, 58.3%), 42.9% (6/14) were treated with IM gel as a first alternative therapy, 21.4% (3/14) with PDT, 14.3% (2/14) with 5% imiquimod, and 14.3% (2/14) underwent surgery; one patient was lost to follow-up (patient 23).

Among patients who were treated with a second cycle of IM gel (42.9%; 6/14) as a first alternative treatment, three of them (3/6, 50%) achieved complete resolution of lesions, and the other three cases (3/6, 50%) were subjected to a third treatment: one patient underwent surgery and resolved clinically; the other two were treated with MAL-PDT but failed to respond (patients 19 and 20; lost to follow-up). Overall, 54.2% of patients (13/24) were successfully cured after one (10/13, 76.9%) or two cycles (3/13, 23.1%) of IM.

Patients treated with PDT (3/14, 21.4%) as a first alternative therapy after NCR with IM, failed to respond favorably. One patient was lost to follow-up (patient 22), and the other two achieved clinical resolution after surgery.

Finally, one patient treated with 5% imiquimod (1/2, 50%) and one patient treated with surgery (1/2, 50%) as first alternative therapies after NCR with IM, showed complete healing. Non-resolved lesions were successfully cured after performing a second alternative treatment with 5% imiquimod.

At the end of the follow-up period (average duration of follow-up: 10.4 months, range 0.5-44 months), 20 of 24 lesions were completely resolved.
Patients who did not respond favorably after two cycles of IM either failed to respond to MAL-PDT (two patients) or resolved after surgery (one patient).

Surgery and 5% imiquimod were partially successful as a first alternative therapy, whereas MAL-PDT was not effective. Refractory cases requiring a second alternative therapy (7 patients) were only resolved with excision surgery (3/7, 42.8%) or topical 5% imiquimod (2/7, 28.6%); when MAL-PDT was applied (2/7 cases, 28.6%), no resolution of lesions was observed. Surprisingly, although there is supportive evidence of superior efficacy and tolerability of PDT compared with conventional treatments [16, 17], our patients did not respond positively to PDT. Maybe the low number of patients being subjected to this treatment and the fact that they underwent a previous treatment with IM may account for these observations.

Our study has several limitations inherent to its retrospective design. Namely, the choice of treatment is subjected to the clinician’s expertise, with decisions potentially being influenced by several factors, such as location and size of the lesions, patient status (age, immune status, concomitant medication, comorbidities and compliance), patient’s preference, and the perceived potential for wound healing [16]. Further investigation is required to overcome these limitations and to provide additional data for the management of BD with IM. So far, since experience of IM for BD has been limited to only one study and some case reports and small series [7-13], there is a need for larger studies and also greater uniformity in the methodologies used to evaluate its effectiveness. The number of patients being treated, dose regimen (with or without occlusion during treatment), time of post-treatment assessment, methods for
the evaluation of skin lesions, and the pretreatments performed should be considered.

Nevertheless, the results reported herein are encouraging and suggest that topical IM gel may be considered as a beneficial treatment option for BD lesions, especially in patients and anatomical sites that are unsuitable for other treatments like surgery. According to previous published data, the efficacy rates observed in this study may be improved by enhancing the absorption of the topical agent into the skin before treatment application [13].

Some advantages of using IM are the simple dosing regimen and the short treating course of IM compared with other self-applied agents, which could improve patient compliance. IM gel could also be potentially considered as a cost-effective topical treatment option for BD, although an economic study would be needed.

In summary, this study adds to the limited data on BD patients treated with IM indicating that topical IM gel is well tolerated and represents an acceptable non-invasive therapeutic approach for the management of BD, particularly in patients who are poor candidates for surgical excision. Retreatment with IM also appears to be a suitable choice when initial treatment fails, although it remains to be determined if IM could represent the first choice in retreatment strategies.

5. Conclusions

The results of this study indicate that topical IM gel may be considered as a safe and beneficial non-invasive treatment option for BD, especially in elderly patients and in areas of poor healing that are unsuitable for other treatments. The acceptable safety profile, short treating course and easy self-application of IM gel may improve patient compliance.

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