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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.

Table 1. *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

Table 1. *Continue.*

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

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	7
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

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

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.

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]. To our knowledge, the present study is the first to include a considerable number of cases of BD treated with IM, with a long-term follow-up period.

In this investigation, we examined the use of topical IM in 24 patients with BD. There was an obvious female preponderance (75% of patients), which is in accordance with the majority of studies [14, 15]. Our results showed that 41.7% of lesions (10/24) were clinically resolved at 3 months post-treatment, whereas 58.3% of patients showed non-complete resolution. In successfully treated patients, we observed complete clinical remission of lesions after a follow-up period of 0.5 to 44 months (mean, 14.1 months). These patients experienced mostly mild to moderate skin reactions, showing an acceptable tolerability profile of IM gel. A repeated treatment with IM of six non-complete responder patients led to three more cases of successful healing. Therefore, we can conclude that 54.2% of patients (13/24) with BD lesions achieved complete resolution after treatment with one or two cycles of IM gel.

These percentages are notably high considering the cure rate observed by Lee DW et al [13]. In their study, they enrolled 17 patients and observed the therapeutic efficacy of IM alone (8 patients) or IM with ablative fractional laser pretreatment (9 patients). Despite 52.9% of patients (9/17) showed complete response after treatment with IM, eight of them were previously exposed to fractional CO_2 laser pretreatment. Thus, only one patient (1/8, 12.5%) treated with IM alone showed complete response, revealing a significant difference in the cure rate compared to our cases (12.5% versus 41.7%, considering one cycle of IM). On the other side, when patients were exposed to multiple treatments with IM the authors did not observe any improvement of lesions. Our results differ from these observations. This may be due to the baseline patients' characteristics and the number of patients being treated.

It is also important to highlight differences in the method of evaluation of the therapeutic response to IM between studies. In our study, post-treatment response was determined by both clinical and histological (skin biopsy) assessment (Figure 1), whereas Lee DW et al [13] based their evaluations only on clinical criteria.

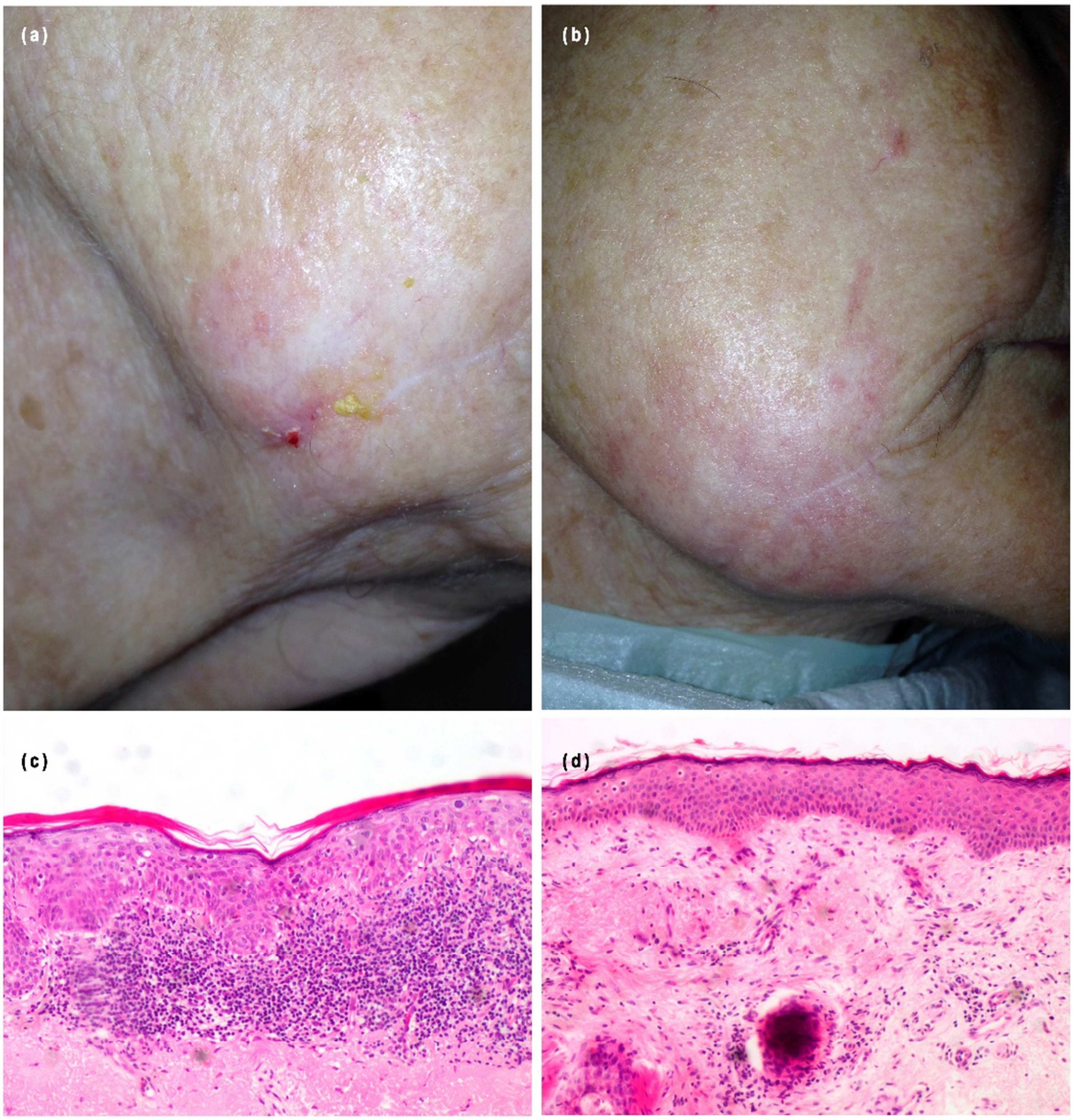

Figure 1. *Bowen's disease mandibular lesion treated with 0.015% ingenol mebutate gel (patient 4). (a) Clinical picture of the lesion before treatment. (b) Clinical picture of the lesion after treatment. The lesion showed complete clearance and no recurrence at 29-month follow-up. (c) Histopathology of the lesion before treatment (Hematoxylin-eosin stain, 20x). (d) Histopathology of the lesion after treatment (Hematoxylin-eosin stain, 20x).*

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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References

[1] Kao GF. Carcinoma arising in Bowen's disease. *Arch Dermatol* 1986; 122:1124–1126.

[2] Jaeger AB, Gramkow A, Hjalgrim H, *et al*. Bowen disease and risk of subsequent malignant neoplasms: a population based cohort study of 1147 patients. *Arch Dermatol* 1999; 135:790–793.

[3] Morton CA, Birnie AJ, Eedy DJ. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014. *Br J Dermatol* 2014; 170(2):245-260.

[4] Neubert T, Lehmann P. Bowen's disease - a review of newer treatment options. *Ther Clin Risk Manag* 2008; 4(5):1085-1095.

[5] Bath-Hextall FJ, Matin RN, Wilkinson D, Leonardi-Bee J. Interventions for cutaneous Bowen's disease. *Cochrane Database Syst Rev* 2013 Jun 24; (6):CD007281.

[6] Morton CA, Birnie AJ, Eedy DJ. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014. *Br J Dermatol* 2014; 170:245–260.

[7] Lee JH, Lee JH, Bae JM, Kim GM. Successful treatment of Bowen's disease with ingenol mebutate 0.05% gel. *J Dermatol* 2015;42(9):920-921.

[8] Alkhalaf A, Hofbauer GF. Ingenol Mebutate 150 mg as Physician-Directed Treatment of Bowen's Disease Under Occlusion. *Dermatology* 2016; 232 Suppl 1:17-19.

[9] Mainetti C, Guillod C, Leoni-Parvex S. Successful Treatment of Relapsing Bowen's Disease with Ingenol Mebutate: The Use of Dermoscopy to Monitor the Therapeutic Response. *Dermatology* 2016; 232 Suppl 1:9-13.

[10] Mohanna MT, Hofbauer GF. Bowenoid Actinic Keratosis and Bowen's Disease Treated Successfully with Ingenol Mebutate. *Dermatology* 2016; 232 Suppl 1:14-16.

[11] Salleras Redonnet M, Quintana Codina M. Ingenol mebutate gel for the treatment of Bowen's disease: a case report of three patients. *Dermatol Ther* 2016; 29(4):236-239.

[12] Kostovic K, Gulin SJ, Mokos ZB, Ceovic R. Topical Ingenol Mebutate: A New Treatment Modality for Multiple Actinic Keratoses and Field Cancerization. *Anticancer Agents Med Chem* 2017; 17(10):1304-1311.

[13] Lee DW, Ahn HH, Kye YC, Seo SH. Clinical experience of ingenol mebutate gel for the treatment of Bowen's disease. *J Dermatol* 2018; 45(4):425-430.

[14] Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease. Br *J Dermatol* 1999; 141(4):633-641.

[15] Kossard S, Rosen R. Cutaneous Bowen's disease: an analysis of 1001 cases according to age, sex, and site. *J Am Acad Dermatol* 1992; 27:406-410.

[16] Truchuelo M, Fernández-Guarino M, Fleta B, *et al*. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions. *J Eur Acad Dermatol Venereol* 2012; 26(7):868-874.

[17] Neubert T, Lehmann P. Bowen's disease – a review of newer treatment options. *Therapeutics and Clinical Risk Management* 2008; 4(5):1085-1095.