Patient's Experience With Imiquimod for Extramammary Paget Disease

Imiquimod, an immune-modulating topical chemotherapeutic agent, has demonstrated considerable efficacy in managing extramammary Paget disease (EMPD). Small sample sizes, inconsistent treatment regimens, and short follow-up periods have precluded definitive conclusions on the efficacy of imiquimod for EMPD. Using a patient-reported survey, we describe the use of imiquimod for EMPD from a patient's perspective to better detail their experience, subjective manifestations, and tolerability.

Methods

We developed an online questionnaire that was distributed to an international, private, online EMPD peer support group. Inclusion criteria specified that responders were prescribed imiquimod at some point during their disease course. The questionnaire queried 4 domains: (1) demographic factors, (2) initial EMPD presentation, diagnosis, and treatment, (3) imiquimod prescribing patterns, regimen, and side effects, and (4) recurrence rates and follow-up.

Results

Of 380 members within the group, 100 (26%) participants responded to the survey. Average age of diagnosis was 61 (range: 24–89) years, 74% were female, and 2% endorsed a family history of EMPD. The most common presenting symptoms include itching (76%), rash (57%), and redness (55%). EMPD most commonly affects the scrotum (67%) in male participants and the labia/vulva (85%) in female participants. Patients most commonly seek care from a gynecologist (69%) or dermatologist (65%). Dermatologists (44%) were the most common prescribers of imiquimod, followed by gynecologist (32%) and surgical oncologists (14%). Before starting imiquimod, many patients had undergone treatment with surgery—wide local excision ($n = 35$, 61%) or Mohs micrographic surgery ($n = 10$, 18%), medical topical skin therapy (30%), or nonmedical therapies (14%) such as lotions and emollients.

Table 1 highlights key findings of our patient-reported survey on imiquimod use and its associated outcomes. The initial application regimen of imiquimod varied significantly among patients. Most patients applied imiquimod 3 days a week as an initial regimen (61%). Treatment was often extended over several months, the most frequent reported duration being 2 to 4 months (37%), followed by > 4 months (31%). Up to 88% of patients experienced side effects, the most common being burning (89%) and pain (60%) at the application site. Thirty-eight percent of patients underwent a change in imiquimod regimen with the most common reason being a reduction in dosing or discontinuation of medication because of local or systemic side effects (81%). Nine percent of patients increased their application regimen because they noticed clinical improvements.

Approximately half the cohort ($n = 44$, 47%) underwent biopsy of the EMPD site during or after their course of imiquimod. Of these, 40% demonstrated no recurrence, 40% demonstrated recurrences, whereas the remaining 20% never completely cleared their disease. Among the entire cohort, 43% ($n = 38$) of patients with EMPD entered remission after imiquimod use. Of those, 84% ($n = 32$) remained in remission for an average of 23 (range: 1–60) months. Some other adjuvant/salvage treatments after imiquimod included surgery (41%), radiation therapy (21%), photodynamic therapy (11%), and laser therapy (6%).

Discussion

The patient-reported prescribing patterns noted in this study highlights the lack of standardized protocols for imiquimod use. This is due to the paucity of Level 1 evidence secondary to the rarity of this disease. Similar to our findings, a recent systematic review also reported many different iterations to imiquimod application regimen with 3 to 4 applications/week being the most common initial frequency (68%) and 4 to 6 months being the most common duration of treatment (41%).[1] Fortunately, the authors reported no significant difference in the rates of complete response, partial response, or disease progression with the different regimens used over a median time of 12 months, even when the frequency was reduced.

The reason the rates of medication discontinuation or reduction from side effects are significantly higher than that reported in the literature may be because our results are driven by patient-reported data, not provider-reported effects.[2] As such, patients should receive anticipatory guidance on side effects with careful monitoring of tolerance and adjustments to application regimen where appropriate.

For patients undergoing concurrent surgery, most of them were prescribed imiquimod postoperatively (35% vs 19% preoperatively). It is not uncommon for patients to have microscopically positive margins after primary surgery because of the multifocal nature of EMPD. In these settings, patients may receive adjuvant therapy with imiquimod to avoid undergoing multiple mutilating re-excisions to the anogenital region, subsequently allowing for preservation of sexual function.[3,4] Some surgeons may be hesitant to prescribe

Dermatol Surg 2023;00:1–2
http://dx.doi.org/10.1097/DSS.0000000000003807

TABLE 1. Key Findings of Our Patient-Reported Survey on Imiquimod Use and Outcomes	
Imiquimod Use	
Application frequency	Between once daily to once every 10 d
Application duration	Between 1 wk to over 7 mo
Side effects	88% of patients experienced burning, pain, and ulcerations to application site
Changes in initial regimen	38% of patients underwent changes, of which 32% underwent a reduction of duration/frequency/dosing
Reasons for regimen change	81% of patients underwent reduction/discontinuation of imiquimod because of local or systemic side effects
Imiquimod outcomes	
Timing of biopsy	Between 1 mo to 1 yr after initiating imiquimod
Biopsy results	40% no recurrence, 40% recurrence, and 20% partial response
Remission data	43% entered remission, of which 84% remained in remission for an average of 23 (range: 1–60) mo
Time to recurrence	Between 1 mo to 2 yr
Progression to locally advanced disease	15 patients reported contiguous spread of disease
Progression to metastatic disease	Present in 2 patients

imiquimod preoperatively because of concerns that it may blur gross margins of the lesion, making intraoperative examinations challenging. Alternatively, others have proposed that preoperative imiquimod use may reduce tumor size and allow for a more conservative surgery resulting in smaller reconstructive area, faster healing times, and overall better functional and cosmetic outcomes.[5] Further studies are necessary to delineate the role of imiquimod therapy as concomitant therapy with surgical interventions for EMPD.

Although the timing of biopsy varied significantly, we reported an 80% ($n = 32$) complete response rate at some point with imiquimod use. Patients also received a wide breadth of treatment modalities after initiation of imiquimod, as well as variable biopsy performance and surveillance schedules. This supports the need for continued long-term follow-up of EMPD after imiquimod therapy.

Our study limitations include the use of a nonvalidated survey to members with access to the online peer support group only. We were limited by geographical distribution, which may result in selection bias. Survey data are also subject to respondent recall bias. Our sample size was small and precluded any significant statistical analyses. The survey omitted EMPD clinical characteristics including tumor size, tumor invasion, primary versus recurrent disease, and timeline of disease recurrence, which are pertinent to the treatment options and clinical outcomes.

Conclusions

As imiquimod has become a more popular treatment option for EMPD, it is important to document patient experiences that come with it. Lack of standardized treatment protocols and variable tolerability results in inconsistencies in use of imiquimod for EMPD. Given the potential for lack of complete clearance and reoccurrence, patients require long-term surveillance and consideration of repeat treatment when using imiquimod as part of their treatment protocol. These finding underscore the need for consensus guidelines to ensure optimal disease outcomes and patient satisfaction.

References

1. Machida H, Moeini A, Roman LD, Matsuo K. Effects of imiquimod on vulvar Paget's disease: a systematic review of literature. *Gynecol Oncol* 2015;139:165–71.
2. Borella F, Preti M, Vieira-Baptista P, Pérez-López FR, et al. Vulvar Paget's disease: outcomes of 51 patients treated with imiquimod cream. *Maturitas* 2022;163:23–7.
3. Liau MM, Yang SS, Tan KB, Aw CW. Topical imiquimod in the treatment of extramammary Paget's disease: a 10 year retrospective analysis in an Asian tertiary centre. *Dermatol Ther* 2016;29:459–62.
4. Cowan RA, Black DR, Hoang LN, Park KJ, et al. A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease. *Gynecol Oncol* 2016;142:139–43.
5. Luyten A, Sörgel P, Clad A, Gieseking F, et al. Treatment of extramammary Paget disease of the vulva with imiquimod: a retrospective, multicenter study by the German Colposcopy Network. *J Am Acad Dermatol* 2014;70:644–50.

Joon Yau Leong, MD*
Andrew Shumaker, BS*
Darren D'mello, BS*
Elizabeth K. Jones, MD†
Paul H. Chung, MD*

**Department of Urology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia Pennsylvania*
†Department of Dermatology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia Pennsylvania

The authors have indicated no significant interest with commercial supporters.