The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Treatment of periocular lentigo maligna with topical 5% Imiquimod: a review

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Lentigo Maligna is a benign subtype of melanoma in situ and can progress to lentigo maligna melanoma, which is invasive. Complete surgical excision is the gold standard of treatment but requires large margins. If affecting the peri-ocular region, surgical excision leads to extensive defects, complex reconstructions, and functional impairment of the protection of the ocular surface. Here we review the reported literature about the use of Imiquimod 5% topical cream for lentigo maligna of the eyelid, the treatment outcomes, side effects and tolerance. In addition, the side effects of imiquimod treatment of non-LM lesions are described to help better inform the decision-making process. Treatment for peri-ocular Lentigo maligna showed a 56–86% complete treatment response and a 90% tolerability rate. However, reported treatment protocols vary and histopathological confirmation of clearance was only obtained in 56%. Further studies are required to determine the optimal treatment protocol to maximise clearance rates. Overall, Imiquimod was well tolerated in the peri-ocular area.

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INTRODUCTION

Lentigo Maligna (LM) is a subtype of melanoma in situ and can progress to lentigo maligna melanoma (LMM). Surgical excision is the gold standard of treatment. However, there can be a large non-pigmented area of the lentigo maligna lesion, which is not clinically apparent on inspection alone. On top of this, surgical clearance frequently requires more than 5 mm margins which leads to extensive defects, complex reconstructions, and high morbidity. Treatment alternatives are required in patients with extensive areas involved or who decline surgical treatment. Imiquimod 5% cream is licensed for treatment of genital warts, actinic keratosis and superficial basal cell carcinomas. Its off-label use is common for non-periocular lentigo maligna. Use on the eyelids is not recommended due to possible side effects to the ocular surface. However, its use in the periocular area has been reported. Here, we therefore review the reported literature about the use of Imiquimod 5% topical cream for lentigo maligna of the eyelids, the treatment outcomes, side effects and tolerance. In addition, the side effects of imiquimod treatment of periocular non-LM lesions are described to help better inform the decision-making process.

LENTIGO MALIGNA

LM is a subtype of melanoma in situ. It is most prevalent in the elderly, fair skinned population. It typically arises as a slowly progressive, variably pigmented macule in sun-damaged skin [1, 2]. In about 78% cases, it is located in the head and neck area [3]. The incidence of LM appears to be significantly rising over recent decades, for example, the age standardised incidence rate for LM has increased from 0.72 to 3.84 per 100,000 person-years from 1989 to 2013 in the Netherlands, while in Denmark it rose from 2.6 to 8.1 cases in women and from 1.4 to 5.6 in men from 1997 to 2011 [4–6].

While LM is benign, it has the potential to progress to invasive disease which is called LMM [1, 7]. LMM has the same prognosis and risk of metastasis and mortality as invasive melanoma [7]. The true progression rate of LM to LMM is unknown. Weinstock and Sober reported a risk of 3.3% for developing LMM by the age of 75 if LM was diagnosed at age 45 compared to a risk of 1.2% if LM was diagnosed at age 65 [8]. A more recent study from 2016 found that the cumulative incidence of LMM after 25-year follow-up was 2.0% for males and 2.6% for females in 10,545 patients with LM [4]. The risk may be underreported as areas of invasion, which were seen in 16% on histopathological examination in a study by Agarwal-Antal et al., may be missed due to low clinical suspicion and lack of biopsy [9]. On the other hand, LM itself is underreported, probably to a greater degree.

To prevent transformation to invasive LMM, the current interdisciplinary European Consensus Guidelines from 2019 recommend complete surgical excision of LM as first-line management. Staged excision has been shown to have higher clearance and less recurrences than wide excision [9]. Mohs micrographic surgery with staged excision (often called "slow Mohs") is reported to show the lowest rate of recurrence with 0.3% after 5 years and 2.2% after 10 years [10, 11].

Unfortunately, due to subclinical spread (with non-pigmented area involvement) and the difficulty of histological differentiation of LM from background atypical melanocytic hyperplasia, the standard surgical margins for clearance are insufficient [12, 13]. Multiple studies have demonstrated that a 5 mm margin is not adequate [9, 11, 14]. Kunishige et al. found 86% of LM was cleared

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with 6 mm margins while 9 mm margins were necessary to achieve a complete excision of 98.7% of LM [10]. Malhotra et al. reviewed mapped serial excisions in 141 cases of LM and LMM. 31% of lesions required more than 5 mm margins and 14% more than 10 mm margins for complete excision. Of these cases, 19% were involving the periocular area [15].

As LM predominantly affects the head and neck region, this extensive surgery can lead to severe cosmetic and functional impairment with associated morbidity, and clearance may be unachievable [12].

Especially in the periocular region, clearance can be exceptionally difficult and impair the most important function of the eyelids, ocular surface protection. Complex reconstructions with the aim to restore eyelid function may be required. Primary acquired melanosis (PAM) of the conjunctiva may be associated as a spillover disease and furthermore complicate clearance by surgery. When LM is located on the eyelids, it is likely that a greater proportion of patients refuse this surgery due to the eyelids' critical function in maintaining sight and the highly noticeable location in the centre of the face. Furthermore, patients with co-morbidities may be unsuitable for surgery.

For these reasons, non-surgical management options are needed. The alternatives include cryotherapy, radiotherapy and topical Imiquimod.

IMIQUIMOD FOR LM

Imiquimod is a topical immune response modifier of the imidazoquinolone drug family [16]. It stimulates the innate and acquired immune pathways which lead to recognition and destruction of viral infected or tumour cells in the skin [17].

The effects of imiquimod are mediated through Toll-like receptors 7 and 8 on cells of the immune system that lead to the release of cytokines and other mediators that trigger an inflammatory cascade [18, 19]. Imiquimod also leads to interferon-gamma production from T helper (Th)-1 cells that stimulate cytotoxic T lymphocytes for a cellular immune response [17, 18]. In addition, Imiquimod may induce tumour cell specific apoptosis independent of membrane-bound death receptors [7, 18].

Imiquimod 5% cream (Aldara^{TM}) has shown efficacy and is licensed in the UK (United Kingdom) and US for the treatment of many conditions including genital warts (three times a week for up to 16 weeks), actinic keratosis (three times a week for one or two 4-week courses, with a 4-week gap) and superficial basal cell carcinoma (five times a week for 6 weeks, applied to the lesion and 1 cm around it), when other treatments cannot be used [20]. The treatment of LM with Imiquimod 5% topical cream in non-periocular areas is off label but commonly used [7]. A common treatment regime for non-periocular areas is once a day for 60 days.

The 2019 guidelines for the management of primary cutaneous melanoma from the American Academy of Dermatology state that topical imiquimod 5% cream may be used as second-line treatment for melanoma in situ, of LM type, when surgery is not possible or when optimal surgery has already been performed (adjuvant). They recommend careful discussion of the associated risks, benefits, and uncertainties of non-surgical treatment [21].

Results of response and recurrence vary due to different treatment regimes, assessment of outcome and duration of follow up. Reports about complete histopathological clearance vary from 37 to 92% [22, 23]. However, Imiquimod treatment protocols are highly variable between published studies. More intensive treatment protocols with multiple applications per week (more than 60 times over 12 weeks) show greater odds of histological clearance [24].

In 2017 Tio et al. systematically reviewed 26 case reports, 11 retrospective studies, 3 prospective studies and one randomised controlled study about the use of topical Imiquimod for LM [24]. They found complete clinical clearance in 78% (369 of 471 patients) and histological clearance in 77% (285 of 370 patients). They report a recurrence rate of LM in 2% after a mean follow up of 18.6 months (range 9–37 months) and a progression to LMM in 1.8% at a mean of 3.9 months (0–11 months) after completion of treatment.

Imiquimod has also been successfully used as neoadjuvant therapy in LM to decrease the necessary margins for complete clearance [25].

Regarding reported adverse effects, a dose-dependent and possibly severe inflammatory reaction can be clinically observed in the treated area that ceases after stopping the treatment. Rarely flu-like symptoms have been observed [7].

The BNF [26] and patient information leaflet for Imiquimod 5% cream recommends avoiding contact with the eye. Therefore, use on the eyelids is not common. However, there are several publications that describe its use on the eyelids for both Lentigo maligna and non-melanocytic lesions such as actinic keratosis, basal cell carcinoma and squamous cell carcinoma.

TREATMENT PROTOCOLS AND SUCCESS RATES OF IMIQUIMOD FOR PERIOCULAR LENTIGO MALIGNA

There have been two case series and four case reports of imiquimod 5% treatment for periocular lentigo maligna published, with 21 patients in total (Table 1).

Elia et al. published the largest study, a retrospective case series of 12 patients with periocular LM treated with topical 5% imiquimod cream over a median treatment period of 3 months (range 1–10 months) [27]. In six patients this was primary treatment, and in the other 6 it was adjunctive treatment following local excision ($n = 2$), cryotherapy ($n = 2$) or both ($n = 2$). Erythromycin ointment was applied to the inferior fornix before using imiquimod to protect the ocular surface. Imiquimod was applied once daily except in one patient who only tolerated application every other day.

One patient discontinued treatment due to side-effects, the remaining 11 patients (92%) showed complete clinical and histological clearance.

Demirci et al. reported a case series of five patients treated with topical 5% Imiquimod for periocular LM over a mean duration of 9 months [28]. If the lesion was located within 5 mm of the lid margins, topical erythromycin eye ointment was applied to the eye before Imiquimod to protect the eye. However, their paper did not specify how many patients fell into this group. They clinically observed partial resolution of lesions in two patients and complete resolution in three patients. Yet, they did not report the post-treatment histological examinations.

Four singular case reports about the treatment of LM involving the eyelid with topical Imiquimod 5% have been published [29–32]. All four cases showed complete clinical resolution of pigmentation with different treatment periods (6 weeks, 2 months, 4 months, and four courses of 6 weeks treatments over 2 years).

Three of those four singular case reports described additional successful treatment of co-existing conjunctival disease.

Bratton et al. combined the treatment of Imiquimod for the eyelid LM with repeated cryotherapy of the periorbital disease, along with guttae interferon-α2β for the associated conjunctival primary acquired melanosis (PAM). The pigmentation of the eyelid skin and conjunctiva completely resolved. No postinterventional histopathology was obtained. 21 months later a mild stippled hyperpigmentation on the conjunctiva reoccurred, that is being observed [29].

Rodríguez-Martín et al. treated a patient with eyelid LM and pigmentation of conjunctiva and caruncle with excisional surgery for the larger skin lesions followed by guttae Mitomycin C for the conjunctival pigmentation and Imiquimod 5% for the caruncle pigmentation. A 6-week course resulted in complete regression of

Table 1. Summary of published cases using treatment with 5% Imiquimod for periocular Lentigo maligna.

Authors	Year	Number of reported cases	Treatment regime	Follow up peroid post treatment	Clearance
Elia et al.	2016	12	Application daily in $N = 11$ Application alternating days $N = 1$ Median Treatment period 3 months (Range 1–10 months) Primary Treatment $N = 6$ Following Local Excision $N = 2$ Following Cryotherapy $N = 2$ Following Local excision and Cryotherapy $N = 2$	Median 18 months (Range 6–60 months)	Complete clinical and histological clearance $N = 11$ (92%) Partial clinical response $N = 1$ (discontinued treatment)
Demirci et al.	2010	5	Application 5×/week ($N = 3$) Application daily ($N = 2$) Mean Treatment period 9 months (Range 1–14 months)	Median 25 months (Range 0–33 months)	Complete clinical response $N = 3$ Partial clinical response $N = 2$
Bratton et al.	2015	1	3×/week for 3 months, then 5×/week for 1 month Combined with Cryotherapy and topical Interferon-α2b for conjunctival PAM with atypia	21 months	Complete clinical response
Murchison et al.	2007	1	5×/week for 2 months	1 month	Complete clinical response
O'Neill et al.	2011	1	5×/week for 4 × 6 weeks over 2 years	36 months	Complete clinical response
Rodríquez-Martín et al.	2010	1	5×/week for 6 weeks Combined with topical Mitomycin C 0,04% 4×/day for 3 months (for conjunctival PAM)	12 months	Complete clinical response

the caruncle lesion with no clinical or histopathological recurrence after 1 year [32].

O'Neill et al. reported clinical clearance of the conjunctival component with Imiquimod to the eyelid skin alone, likely from spillover of the ointment applied to the skin onto the conjunctiva. After 3 years there were no clinical signs of recurrence of both the skin pigmentation and conjunctival pigmentation. However, no histological assessment was performed [31].

In total, 21 patients with periocular lentigo maligna treated with Imiquimod 5% have been published [27–32]. However, the treatment protocols in the reported cases vary considerably, making it difficult to interpret the most beneficial regime with the least side effects. In addition, some patients received combined treatments with surgical excision, cryotherapy, topical Interferon-αhβ or topical Mitomycin C. This makes assessment of the efficacy of Imiquimod treatment more difficult.

The dermatology literature shows that complete treatment success of LM with imiquimod is more likely when more than 60 applications are made over 12 weeks [24].

57% (12/21) of patients included in this review received periocular imiquimod in this recommended regime, suggesting that this could be a useful initial prescribing regime, with the caveat of close monitoring by an ophthalmologist.

Overall, the cases showed a 86% (18/21) clinical clearance rate, albeit only 56% ($N = 12$) had histological post treatment confirmation of clearance, and none had confocal microscopy follow up. This periocular LM success rate with imiquimod treatment is reassuringly similar to the histological clearance rates of 77% [13] with off-label Imiquimod in non-periocular LM lesions. This means that Imiquimod is a very encouraging second-line treatment to that of surgical excision in the periocular area.

SIDE EFFECTS OF IMIQUIMOD TREATMENT FOR EYELID LESIONS

It is important to establish the safety of Imiquimod 5% for lesions of the eyelid, as it is designed to be applied to the skin and not the ocular surface. However, when applied near the lid margin, it is likely that a small amount reaches the ocular surface.

In total, imiquimod has been used periocularly in 81 published cases (21 for lentigo maligna and 60 non-melanocytic lesions) [27–42]. Table 2 details those 16 publications which describe the use of periocular imiquimod and the reported side effects.

The main side effects of imiquimod described were redness (72/81)(not reported if ocular or skin), discomfort (18/81) (not reported if ocular of skin), conjunctival redness/chemosis/conjunctivitis (9/81), swelling (9/81), excoriation/crusting at the application site (9/81). Corneal staining was observed in five cases, epiphora in three cases and a preseptal cellulitis in two cases. There was one reported case each of a staphylococcal keratitis, temporary corneal oedema, ectropion.

73 (90%) patients were able to tolerate treatment and complete their prescribed course. Although 7 (8.6%) needed a treatment holiday (range 3 days to 4 weeks) to reduce side effect severity, and one (1.2%) needed a dose reduction. There was also one non-responder.

These cases have demonstrated safe use in all, and in the majority a tolerable use of 90% (73/82) of topical Imiquimod 5% on the lid margin. Only 9.9% (8/81) of patients had to stop treatment due to intolerable side effects and a further 8.6% required a treatment holiday. Reassuringly all side effects completely resolved once treatment was ceased.

Redness and irritation or even excoriation with crusting of the skin at the application site is to be expected with imiquimod treatment and is believed to indicate a good efficacy of the treatment [27]. Patients without any local reactions are more likely to be poor or non-responders with a lower rate of complete treatment success. It is therefore questionable whether this should

Table 2. Summary of side effects and paused/discontinued treatment of published cases using periocular Imiquimod 5% cream periocularly (AK Aktinic keratosis, BCC Basal cell carcinoma, BD Bowen´s disease, LM Lentigo maligna, SCC Squamous cell carcinoma, UK unknown).

Authors	Year	Number of reported cases	Treatment regime	Pathology	Side effects	Discontinued treatment
Cannon et al.	2011	47	3×/week for 4–6 weeks	AK, BD, BCC, SCC	Erythema at the application side $N = 47$ Conjunctivitis $N =$ UK ocular irritation $N =$ UK Staphylococcal keratitis $N = 1$ preseptal cellulitis $N = 2$	Permanently $N = 5$ (due to ocular irritation and conjunctivitis) Temporary treatment holiday $N = 4$
Ross et al.		5	5×/week for 6 weeks	AK, BD, BCC, SCC	Chemical conjunctivitis $N = 1$ Other $N =$ UK	No (but dose reduction to 2×/week in $N = 1$)
Brannan et al.	2005	1	2×/day every alternate days for 4 weeks, then 1×/day every alternate days for 8 weeks	Bowen´s disease	Inflammation and irritation $N = 1$ After 1 months bi-daily treatment	No (but dose reduction, see treatment regime)
Choontanom et al. and Prokosch et al. (same patient group in 2 publications)	2007 and 2010	5	5×/week for 6 weeks	BCC	Erythema, significant inflammation, irritation, excoriation and crusting $N = 4$ Conjunctivitis $N = 2$	$N = 1$ (non-responder after 2 weeks)
Blasi et al.	2005	2	5×/week for 8 weeks and 12 weeks respectively	BCC	Mild discomfort $N = 1$ Erythema $N = 2$ Conjunctival hyperaemia $N = 1$ superficial punctate keratitis $N = 1$ Erosion and crusting of lesion $N = 2$	Temporary treatment holiday $N = 1$ (2 weeks duration)
Karabulut et al.	2017	3	5×/week for 12 weeks	BCC	Erythema $N = 3$ Erosion of lesion $N = 3$ Conjunctival injection $N = 3$ Burning and itching sensation $N = 3$ Epiphora $N = 3$ Punctate keratitis $N = 3$	No
Leppälä et al.	2007	4	5×/week for 6 weeks	BCC	Significant Inflammation $N = 3$	No
Rowlands et al.	2017	1	5×/week for 6 weeks Erythromycin ointment on treatment free days	AK involving the fornix/ pretarsal conjunctiva	Ocular irritation $N = 1$	Temporary treatment holiday twice (3 and 5 days duration respectively)
Singh et al.	2019	1	2×/day every alternate days for 12 weeks	SCC involving the pretarsal conjunctiva, inferior fornix and caruncle	Conjunctival congestion $N = 1$ Periorbital erythema $N = 1$ Intermittent bleeding episodes $N = 1$	No
Demirci et al.	2010	5	Application 5×/week ($N = 3$) Application daily ($N = 2$) Mean Treatment period 9 months (Range 1–14 months)	LM	Redness $N = 4$ Swelling $N = 3$ Discomfort $N = 4$ Excoriation of skin $N = 2$	Permanently $N = 1$ (After 1 month) Temporary treatment holiday of 1 month (after 3 months) $N = 1$

Table 2. continued

Authors	Year	Number of reported cases	Treatment regime	Pathology	Side effects	Discontinued treatment
Elia et al.	2016	12	Application daily in $N = 11$ Application alternating days $N = 1$ Median Treatment period 3 months (Range 1–10 months) Primary Treatment $N = 6$ Following Local Excision $N = 2$ Following Cryotherapy $N = 2$ Following Local excision and Cryotherapy $N = 2$	LM	Redness $N = 12$ Swelling $N = 4$ Discomfort $N = 6$ Chemosis $N = 1$ Ectropion $N = 1$	Permanently $N = 1$ (after 1 month)
Bratton et al.	2015	1	3×/week for 3 months, then 5×/week for 1 month Combined with Cryotherapy and topical Interferon-α2b for conjunctival PAM with atypia	LM	No adverse side effects	No
Murchison et al.	2007	1	5×/week for 2 months	LM	Significant erythema and crusting corneal oedema and staining with reduced visual acuity (Fully resolved 1-month post-treatment)	No
O'Neill et al.	2011	1	5×/week for 4×6 weeks over 2 years	LM	No adverse side effects	No
Rodríquez-Martín et al.	2010	1	5×/week for 6 weeks Combined with topical Mitomycin C 0,04% 4x/day for 3 months (for conjunctival PAM)	LM	temporary conjunctival and cutaneous irritation and eyelid oedema	No

be included in the side effects if not requiring a treatment pause, and because of this, it was inconsistently reported across all of the publications.

This review suggests that the small amount of Imiquimod that is likely reaching the ocular surface is well tolerated. If, however, a mistake occurs and a large volume of Imiquimod is applied directly to the ocular surface, it would seem sensible to irrigate the eye with saline or lubricants to reduce the risk of ocular toxicity. It seems sensible to follow Elia et al. [27] and Demirci et al. [28] by prescribing an ocular ointment to be used prior to imiquimod application, such as chloramphenicol or a lubricating ointment, to create a protective barrier for the ocular surface. However, a prospective trial would be needed to clearly demonstrate any benefit in side effect reduction.

The timing of the treatment holiday, cessation or dose reduction was only reported clearly in four patients. This was needed at 1 month in three cases and at 3 months in the other case. This suggests that an ophthalmic examination at 3–4 weeks into treatment is imperative.

CONCLUSION

With a rising incidence of LM, second-line treatment options need to be investigated especially if patients are unfit for or decline surgical management [4–6].

Current literature on retrospective cases shows that 5% imiquimod is a promising treatment modality with a 56–86% complete treatment response and a 90% tolerability rate in the peri-ocular area. In the dermatological literature, Tio et al. found a recurrence of LM after Imiquimod treatment in 2% after a mean follow up of 18.6 months (range 9–37 months) [13].

Importantly, 5% imiquimod offers a superior cosmetic outcome to that of surgical excision, can be used in patients with systemic co-morbidities, is easy to use at home [24], and does not preclude future surgical excision should treatment be unsuccessful or not tolerated.

Further studies are required to assess the optimal treatment protocol to maximise clearance rates of periocular LM with topical 5% imiquimod but with minimal ocular side effects. However, this review shows that 60 applications over 12 weeks (as recommended in non-periocular skin) can be tolerated in many. Treatment holidays or dose reductions should be utilised to enable course completion.

As disease recurrence can occur despite initial clearance of LM [43, 44], follow up is essential. This ideally should ideally include confocal microscopy [45], however this is technically difficult close to the lid margin. When in doubt, repeat biopsies must be performed.

Concerns remain regarding clinical clearance of the pigmentation without histological clearance due to potentially unrecognised progression of the disease. There is speculation that Imiquimod has a limited effect on hair follicles, which is especially important for eyelid LM as the eyelash line is thought to be a source of recurrence [28]. Vice versa, residual pigmentation does not necessarily mean residual LM [46]. Therefore, post-treatment biopsies or at least confocal microscopy, which has been reported to be a useful screening tool with significant correlation to biopsies [45], seem imperative, rather than clinical inspection alone.

Tio et al. recommended a 5 year follow up [13]. Albeit they recommend a follow up for 5 years. Thus, post treatment monitoring is required to cover this period.

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AUTHOR CONTRIBUTIONS

IN: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper, Other contribution; HT: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper, Other contribution; RP: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper, Other contribution; MK: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper, Other contribution; CD: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper, Other contribution.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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