

# Imiquimod-side effects in the treatment of periocular skin cancers: A review of the literature

Dear Editor,

Imiquimod (IMQ) is currently approved in Europe for the treatment of adult external genital warts, superficial basal cell carcinoma (sBCC) and actinic keratosis (AK).<sup>1</sup> The majority of non-melanoma skin cancers (NMSC) appear on the head and the neck region and a huge number of NMSC involves the periocular region.<sup>2</sup> This latter localization being close to the eyes might make clinicians hesitate to use IMQ, although severe ocular side effects during treatment with IMQ have not been reported in the literature so far. Anyway, some authors suggested to avoid IMQ's contact with the eyes in order to prevent ocular side effects while other studies show its efficacy without complications.<sup>3</sup> Since the side effects are generally reversible after discontinuation,<sup>4</sup> nonsurgical therapies like IMQ may be a potential useful alternative in these cases. Accordingly, we conducted a review of the literature aiming to provide an extensive overview of the safety, tolerability and efficacy of IMQ when applied in the periocular area, gathering all the cases reported so far.

Demographic information, tumor characteristics, type of management and clinical outcomes of patients treated with periocular IMQ have been summarized (Table 1).<sup>1-9</sup> A total of 175 patients was reported (109 males, 61 females, 5 not specified<sup>3</sup>) with a mean age of 71.27 years old (range 9–95 years). Overall, 180 periocular lesions treated with IMQ have been counted: 106 BCCs, 41 AK, 20 MIS, 11 Bowen's diseases, and 2 cSCCs. As expected, the lower eyelid was

the area most frequently affected by tumors, being involved in 63.74% of cases. The medial canthus was affected in 26.90% of cases, followed by the upper eyelid in 9.36%, and lateral canthus in 8.77%. Eight lesions extended to affect two regions of the periocular area, while 4 lesions involved three parts of it extending themselves over the ocular perimeter. Nineteen tumors compromised the ocular structures or were very close to them. Ocular side effects were described in approximately half of the patients and, where specified, they follow IMQ administration after the first applications or within the first month of treatment.<sup>3</sup> Almost all authors reported that the most frequent IMQ-related ocular manifestations were ocular irritation and conjunctivitis ( $n = 36$ ), followed by blink discomfort ( $n = 15$ ), keratitis, preseptal orbital cellulitis ( $n = 2$ ), ectropion ( $n = 2$ ), chemosis ( $n = 2$ ), temporary decreased of visual activity ( $n = 1$ ), inflammation of prior pterygium ( $n = 1$ ), and slight depigmentation and madarosis ( $n = 1$ ). The most frequent treatment schedule was five applications per week with a mean treatment length of 8.23 weeks (range 4–16 weeks). In case of ocular side effects, a rest period and/or application of ocular support measures were preferred instead of the reduction of IMQ applications.<sup>1,3,8</sup> A complete response was observed in about 80% of all lesions with a mean follow-up period of approximately 20 months.

To the best of our knowledge, this is the first review to collect all the article related to IMQ use in the periocular region reported so far. Although IMQ cream has generally been applied with cotton swabs to

**TABLE 1** Patient's demographics variables and ocular side effects reported following periocular imiquimod administration

Author, year	No. of patients	Sex (M/F) and age (years)	Lesion type and location	Treatment schedule	Clinical response - follow-up time	Ocular side effects
Blasi et al <sup>3</sup> (2005)	2	M, 80 F, 82	- nBCC of lower eyelid margin -nBCC of medial canthus	3 times per week for 8 and 12 weeks	CR—1 year	- 1 superficial punctate keratitis and conjunctival hyperemia after the first week of treatment
Brannan et al <sup>3</sup> (2005)	1	M, 75	Bowen's disease of lower eyelid	2 times a day, every other day (then changed to once a day due to inflammation) for 3 months	CR—34 weeks	-
Tsang et al <sup>3</sup> (2006)	1	M, 40	Bowen's disease of lateral lower eyelid margin	3 times per week for 6 weeks	CR—12 months	Mild ocular irritation

(Continues)

**TABLE 1** (Continued)

Author, year	No. of patients	Sex (M/F) and age (years)	Lesion type and location	Treatment schedule	Clinical response - follow-up time	Ocular side effects
Leppälä et al <sup>3</sup> (2007)	4	M, 85 F, 77 M, 76 M, 89	4 nBCCs	5 times per week for 6 weeks	CR—26 weeks	-
Choontanom et al <sup>3</sup> (2007)	5	M, 36 M, 79 M, 72 M, 63 M, 57	5 nBCCs: —3 of lower eyelid —2 of medial canthus	5 times per week for 6 weeks	—4 CR—42 months on average —1 NR	2 Conjunctivitis
Murchison et al <sup>3</sup> (2007)	1	F, 85	MIS of lateral canthus	5 times per week for 8 weeks	CR—1 month	Chemosis lateral palpebral conjunctiva Punctate keratopathy Corneal edema Temporary decreased of visual activity
Garcia-Martin et al <sup>3</sup> (2010)	15	10 M/5F, (mean age 71, range 53–84 years)	16 nBCCs: —2 of medial canthus —2 of lateral canthus —1 of upper eyelid —11 of lower eyelid (4 on the eyelid margin)	5 times per week for 6 weeks (except 1 patient treated with IMQ for 2 further weeks)	CR—28 months on average	7 patients affected: —6 blink discomfort after 4 weeks —1 inflammation of prior pterygium —1 superficial keratitis associated with conjunctival hyperemia after 5 weeks —2 conjunctival irritation
Demirci et al <sup>3</sup> (2010)	5	F, 71 M, 81 F, 82 F, 62 M, 67	5 LM: - 2 of upper eyelid, medial canthus, and lower eyelid —2 of lower eyelid, lateral canthus area, upper eyelid —1 of medial canthus and lower eyelid	5 to 7 times per week for 1 to 22 months	—3 PR—10 and 29 months —2 CR—25 and 33 months	-
Rodríguez-Martín et al <sup>3</sup> (2010)	1	M, 74	LM of bulbar, lower palpebral, tarsal conjunctiva of the right eye and caruncula lacrimalis <sup>a</sup>	5 times per week for 6 weeks	CR—1 year	Conjunctival irritation
Ross et al <sup>3</sup> (2010)	5	M, 49 M, 72 F, 75 F, 47 M, 79	—2 Bowen's diseases of lower eyelid -AK of lower eyelid -BCC of lower eyelid -sBCC of lower eyelid - cSCC of upper eyelid	5 times per week for 6 weeks (1 patient decreased the treatment to twice per week due to ocular side effect)	CR—10 months	—1 chemical conjunctivitis
Carneiro et al <sup>3</sup> (2010)	8	7 M/1F (mean age 63, range 47–72 years)	10 nBCCs: - 6 of medial canthus - 4 of lower eyelid	5 times per week for 10 to 16 weeks	—8 CR—11.7 months on average —2 PR—11.7 months on average	Keratitis punctata and allergic conjunctivitis

**TABLE 1** (Continued)

Author, year	No. of patients	Sex (M/F) and age (years)	Lesion type and location	Treatment schedule	Clinical response - follow-up time	Ocular side effects
Cannon et al <sup>3</sup> (2011)	47	26 M/21F (mean age 74, range 42–95 years)	37 AK, 7 Bowen's diseases, 3 BCCs: –34 of lower eyelid –8 of medial canthus –4 of upper eyelid –4 of lateral canthus Three lesions were present in more than 1 location	3 times per week for 4–6 weeks	–34 CR—16 weeks on average –12 PR/NR –1 lost at follow-up	- 15 conjunctivitis (in 3 patients after a mean of 2.3 weeks) –6 ocular stinging - 2 preseptal orbital cellulitis –1 microbial keratitis –1 cicatricial ectropion which required surgical intervention
Prokosh et al <sup>3</sup> (2011)	5	M, 63 M, 72 M, 57 M, 79 M, 36	–5 nBCCs of lower eyelid (2 involving the eyelid margin)	5 times per week for 6 weeks	- 4 CR—7 years –1 refused to continue IMQ due to discomfort	–2 conjunctival injection mostly due to accidental contact of the cream with conjunctiva –1 slight depigmentation and madarosis
Garcia-Martin et al <sup>3</sup> (2011)	15	10 M/5F (mean age 73, range 53–84 years)	15 nBCCs: –2 of lateral canthus (one involving eyelid margin) –2 of medial canthus - 9 of lower eyelid (4 in eyelid margin) –2 of upper eyelid	5 times per week for 6 weeks	CR—24 months	After 4 weeks of treatment: –2 intense conjunctival irritation –9 blink discomfort
O'Neill et al <sup>3</sup> (2011)	1	F, 62	LM of lateral canthus extending to the conjunctiva	5 times per week for 6 weeks (4 cycles of IMQ administered over 2 years)	CR—3 years	-
Gaitanis et al <sup>3</sup> (2011)	3	- M, 68 - M, 69 - F, 75	3 BCCs: –1 of lower eyelid –1 of medial canthus –1 of medial canthus infiltrating the caruncula lacrimalis	1 time a day in combination with cryosurgery every 2 or 3 weeks, for 7 to 9 weeks	CR—10 months on average	-
Attili et al <sup>3</sup> (2012)	12	M7/F5 (mean age 70, range 59–85 years)	11 BCCs and 2 AK: - 6 of lower eyelid - 3 of medial canthus –2 of lateral canthus - 1 of upper eyelid - 1 of lower eyelid and lateral canthus	3 to 5 times per week for 6 weeks	- 8 CR—34 months - 3 PR - 2 NR due to discontinuation of IMQ for local irritation	- 2 conjunctivitis after 2 and 4 IMQ applications respectively
Bonilla et al <sup>5</sup> (2014)	5	-	5 nBCCs of the periocular area not involving the lid margin	5 times per week for 4 weeks	PR following by surgical excision	-

(Continues)

**TABLE 1** (Continued)

Author, year	No. of patients	Sex (M/F) and age (years)	Lesion type and location	Treatment schedule	Clinical response - follow-up time	Ocular side effects
De Macedo et al <sup>2</sup> (2015)	19	M13/F6 (5 patients <60 years, 9 patients 60–70 years, 5 patients >70 years)	19 nBCCs: - 8 of lower eyelid - 11 of medial canthus	5 times per week for 8 to 16 weeks	- 16 CR—3 years - 3 PR—3 years - One patient interrupted treatment for 2 weeks due to adverse effects (the only patient with tumor recurrence 2 years after treatment)	Conjunctivitis (95%), keratitis (84%), foreign body sensation (79%), lacrimation (58%), low visual acuity (53%), and ectropion (37%)
Elia et al <sup>4</sup> (2016)	12	M6/F6 (mean age 77, range 65–88 years)	12 MIS - 6 of lower eyelid - 1 of lower eyelid including the lid margin - 1 of medial canthus - 3 of upper and lower eyelid - 1 of brow	1 time a day (except for a patient treated 1 time every other day) for a median treatment length of 3.9 months, following local excision ( <i>n</i> = 2), cryotherapy ( <i>n</i> = 2), or excisional biopsy with cryotherapy ( <i>n</i> = 2)	- 11 CR—1.5 years on average - 1 discontinued IMQ due to local irritation	- 1 conjunctival chemosis - 1 ectropion after 3 months
Rowlands et al <sup>8</sup> (2017)	1	M, 68	AK involving the lower eyelid pretarsal conjunctiva, surrounding the punctum, and the eyelid margin	5 times per week for 6 weeks	CR	Ocular irritation
Costales-Álvarez et al <sup>6</sup> (2017)	2	F, 95 M, 52	- BCC of medial canthus - BCC of lower eyelid	5 times per week for 6 weeks	CR—6 months	-
Agarwal et al <sup>7</sup> (2017)	1	M, 9	nBCC of medial canthus	5 times per week for 8 weeks	PR—90% reduction after 7-months follow-up	-
Karabulut et al <sup>1</sup> (2017)	3	M2/F1 (mean age 56, range 45–73 years)	Three nBCCs of medial canthus	5 times per week for 16 weeks	- 2 CR—2 years - 1 PR following by surgical excision	3 punctate keratitis with conjunctival hyperemia
Singh et al <sup>9</sup> (2019)	1	M, 84	cSCC of lower eyelid involving the conjunctiva, caruncula lacrimalis, and punctum, causing mechanical ectropion and eversion of the lower eyelid	2 times a day, every other day, for 12 weeks	CR—6 months	Transient conjunctival congestion

Abbreviations: AK, actinic keratosis; CR, complete response; cSCC, cutaneous squamous cell carcinoma; F, female; LM, lentigo maligna; M, male; MIS, melanoma in situ; nBCC, nodular basal cell carcinoma; NR, no response; PR, partial response; sBCC, superficial basal cell carcinoma.

<sup>a</sup>IMQ was applied only on caruncle area.

avoid drug contact with cornea or conjunctiva, ocular side effects have been developed in about half of the cases described (47.31%;79/167). However, IMQ application in the periocular region has been generally well-tolerated by almost all the patients receiving the treatment. Overall, side effects appear to be not severe and tend to be reversible after IMQ discontinuation. No recurrences have been observed. On the basis of collected data, the absence of important side effects makes IMQ a promising therapeutic option for the treatment of skin tumors on the periocular region. Dermatologists and ophthalmologists should collaborate to better target and manage any IMQ-related periocular adverse manifestation.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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