impact medical journals: interrupted time series analysis. BMJ 2012; **344**:e4178.

Funding sources: none.

Conflicts of interest: M.L.M., A.C.B., S.H.V. and A.W.C. declare they have no conflicts of interest. A.M.D. has received compensation from the British Association of Dermatologists (reviewer and section editor), American Academy of Dermatology (guidelines writer) and National Eczema Association (grant reviewer). He has been a paid consultant for the Canadian Agency for Drugs and Technology in Health. He has received honoraria from CME Outfitters.

Real-world experience of off-label use of imiquimod 5% as an adjuvant therapy after surgery or as a monotherapy for lentigo maligna

Dear Editor, As lentigo maligna (LM) has a tendency for subclinical extension, staged excisions with margin control achieve lower recurrence rates than conventional wide local excision (0–9·5% vs. 8–20%).[1,2] However, these surgical techniques are limited by the requirements of time, cost and training.

Imiquimod 5% has been used off-label for the treatment of LM with cure rates ranging from 50% to 100%.[3–5] Other studies also assessed its use as an adjuvant or a neoadjuvant therapy combined with surgery.[6,7]

We report real-world evidence on imiquimod used for the treatment of LM either in combination with surgery or as a primary treatment between 2015 and 2019 in seven centres in Austria, France, Greece and Italy. All patients included in this study had been treated on an individual basis according to the preferences of their clinician and data were collected retrospectively.

The included patients were categorized into three groups. Group 1 (adjuvant) comprised patients who underwent surgical excision with narrow clinical margins (< 5 mm, subgroup 1a) or wider margins (≥ 5 mm, subgroup 1b), and were histopathologically assessed as clear of tumour, and then received imiquimod. Group 2 (complementary) comprised patients who underwent surgical excision with narrow clinical margins (< 5 mm), which were histopathologically assessed as involved, and then received imiquimod. Group 3 (primary) was composed of patients with biopsy-confirmed LM, which was not surgically excised for any reason, who received imiquimod as a primary treatment.

Descriptive statistics or frequencies were calculated for all variables. Multivariate Cox proportional hazards regression was used to assess the effects of covariates on time variables (α level was set at 0·05). Analyses were performed using SPSS 23·0 (IBM, Armonk, NY, USA).

Overall, 149 patients were included. Patient demographic characteristics and tumour baseline characteristics for each study group are shown in Table 1. The baseline characteristics did not differ between groups 1 and 2. The difference in mean age, mean diameter and percentage of recurrent tumours between group 3 and groups 1 and 2 were significant ($P < 0·01$). The regimen used in all patients was imiquimod 5% cream applied 7 days per week, with a mean duration of 6–13 weeks.

Recurrence rates in groups 1 and 2 and response rates in group 3 are shown in Table 1. All recurrences were histopathologically confirmed. In a multivariate Cox regression model, every added millimetre of lesion diameter increased the adjusted probability of recurrence by 18%, which is consistent with previous evidence suggesting an increased subclinical extension in larger LMs.[8] A robust (grade III) inflammatory reaction was associated with 13-fold higher odds of complete clinical response in group 3.

The recurrence rate of LM treated with adjuvant imiquimod after surgical excision was 5·6% at a mean follow-up of 32·5 months. This is lower than previously reported recurrence rates of LM following conventional surgery (8–20%), and closer to the recurrence rates achieved with staged margin control methods (up to 0–9·7%).[1–5] A previous study assessed imiquimod as an adjuvant treatment following surgery, applied to narrow histopathologically clear margins or to histopathologically involved margins but without clinical residual tumour. At a mean follow-up of 42·1 months, the researchers found a 5·6% recurrence rate, which is remarkably similar to our findings.[6] Based on a similar concept, imiquimod has also been assessed as a neoadjuvant modality before surgery. The largest cohort study found a recurrence rate of 3·9% at a mean follow-up of 5·5 years.[7]

Notably, in our study, wider excision (≥ 5 mm margins) prior to imiquimod application did not result in a lower recurrence rate (6·2%) compared with narrower (< 5 mm margins) excision (5·5%). This cumulative evidence suggests that imiquimod applied to narrow margins before or after conventional surgery may result in acceptable recurrence rates, possibly comparable with those achieved with surgical techniques involving complete margin assessment, such as Mohs micrographic surgery and staged excision with permanent sections. However, this hypothesis should be assessed by a randomized trial. This alternative treatment strategy could be clinically appropriate for patients who are poor candidates for advanced surgery or in settings where these procedures are unavailable.

In the group of LMs excised to histopathologically involved margins (group 2), the recurrence rate in our sample was 9·1% at a mean follow-up of 34 months. In this group, imiquimod was used for a mean of 7·9 weeks and the recurrence rate could have been lower if imiquimod was applied for a longer period. Cumulative imiquimod dose and treatment intensity with at least 60 applications for ≥ 5 days per week were shown to increase imiquimod efficacy when used as a monotherapy for LM.[4,5] Therefore, prolongation of the treatment could have a similar favourable effect also in the adjuvant setting.

Table 1 Data for 149 patients with lentigo maligna treated with imiquimod 5% in seven centres

	Group 1a (adjuvant after narrow excision) (n = 55)	Group 1b (adjuvant after wide excision) (n = 16)	Group 1 total (adjuvant after excision) (n = 71)	Group 2 (complementary) (n = 22)	Group 3 (monotherapy) (n = 56)
Mean (SD) age (years)	73·0 (10·5)	69·5 (7·9)	72·0 (10·1)	67·0 (12·7)	80·7 (8·6)
Sex					
Male	29 (53)	11 (69)	40 (56)	10 (45)	31 (55)
Female	26 (47)	5 (31)	31 (44)	12 (55)	25 (45)
Location					
Scalp	4 (7)	3 (19)	7 (10)	1 (5)	3 (5)
Ear	3 (6)	1 (6)	4 (6)	2 (9)	3 (5)
Forehead	9 (16)	0 (0)	9 (13)	0 (0)	4 (7)
Temple	1 (2)	1 (6)	2 (3)	1 (5)	3 (5)
Orbital	1 (2)	2 (13)	3 (4)	2 (9)	2 (4)
Cheeks	29 (53)	8 (50)	37 (52)	9 (41)	30 (54)
Nose	5 (9)	1 (6)	6 (9)	4 (18)	11 (20)
Perioral	3 (6)	0 (0)	3 (4)	3 (14)	0 (0)
Mean (SD) diameter (mm)	10·0 (6·1)	12·7 (6·0)	10·6 (6·1)	10·8 (7·3)	18·4 (12·5)
Primary or recurrent					
Primary	44 (80)	13 (81)	57 (80)	17 (77)	35 (63)
Recurrent	11 (20)	3 (19)	14 (20)	5 (23)	21 (37)
Mean (SD) treatment duration (weeks)	6·0 (0·9)	6·1 (1·2)	6·0 (1·0)	7·9 (2·7)	13·0 (7·1)
Recurrence					
No	52 (94)	15 (94)	67 (94)	20 (91)	–
Yes	3 (6)	1 (6)	4 (6)	2 (9)	–
Mean (SD) follow-up after treatment (months)	35·6 (15·6)	21·6 (10·1)	32·5 (15·6)	34·0 (13·6)	33·6 (20·2)
Median recurrence-free survival (months)	58·3 (1·5)	38·0 (1·8)	56·3 (1·35)	50·9 (2·7)	–
Inflammatory reaction					
None	10 (18)	2 (13)	12 (17)	1 (5)	4 (7)
Grade I	27 (49)	11 (69)	38 (54)	8 (36)	12 (21)
Grade II	16 (29)	2 (13)	18 (25)	10 (46)	21 (38)
Grade III	2 (4)	1 (6)	3 (4)	3 (14)	19 (34)
Response					
None	–	–	–	–	4 (7)
Partial	–	–	–	–	12 (21)
Complete	–	–	–	–	40 (71)

Data are presented as n (%) unless otherwise stated.

Imiquimod monotherapy resulted in complete clinical response in 71·4% of treated patients, consistent with previous studies.[3–5] These findings (and those of other studies) support surgery as the primary treatment for LM in operable patients, not only because of the higher cure rates, but also because it allows for complete histopathological evaluation and detection of possible microinvasion.

The main limitations of the current analysis are the heterogeneous dataset, derived from individually treated patients and not from a study protocol, and the limited follow-up period that poses a risk of missing late recurrences.

In conclusion, imiquimod is used in clinical settings in combination with conservative surgery for LM, and the real-world experience is encouraging.

A. Lallas,[1,2] E. Moscarella,[3] H. Kittler,[4] C. Longo,[5,6] L. Thomas,[7,8,9] I. Zalaudek,[10] A. Kyrgidis,[11] S.M. Manoli,[1,2] N. diMeo,[10] C. Papageorgiou,[2,12] Z. Apalla[2,12] and G. Argenziano[3]

[1]First Department of Dermatology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece; and [2]DERMOMEDICA Dermatology Unit, Thessaloniki, Greece
Email: emlallas@gmail.com

The full list of author affiliations is available in Appendix S1 (see Supporting Information).

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Funding sources: none.

Conflicts of interest: the authors declare they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full list of authors and affiliations.

Topical tofacitinib for the treatment of alopecia areata affecting facial hair

DOI: 10.1111/bjd.20419

Dear Editor, Alopecia areata (AA) is a common autoimmune condition which can affect any hair-bearing site. Recent studies have demonstrated the effectiveness of Janus kinase (JAK) inhibitors in the treatment of AA. Most studies documenting response of AA affecting facial hair to JAK inhibitor therapy involve oral administration due to extensive concomitant scalp involvement.[1,2] However, oral JAK inhibitors are associated with adverse effects, such as infections, in 2–6% of patients.[3] Topical JAK inhibitors may offer a safer alternative for limited disease, or in cases where systemic therapy is contraindicated or not desired.[3–5] To our knowledge, published reports on the use of topical JAK inhibitors in eyebrow and eyelash AA are limited to a small number of cases,[3–5] and none have investigated their effectiveness for beard AA. Our objective was to evaluate the response of AA affecting facial hair to topical tofacitinib.

We retrospectively reviewed the records of all patients with eyebrow, eyelash and/or beard AA who were treated with topical tofacitinib between October 2014 and January 2021. Patients treated with topical tofacitinib (2% gel twice daily for eyebrow and beard AA, or 0·005% eye drops once daily for eyelash AA) for $\geq$ 3 months were included. Tofacitinib was compounded into a 2% poloxamer gel or a 0·005% aqueous solution by a local pharmacy. Patients who received concomitant topical or intralesional therapies, such as corticosteroids, were excluded. Of the patients also receiving systemic therapies, only those without treatment changes in the previous 6 months were included. Clinical involvement and response were evaluated at baseline and post-treatment using standardized photographs. Eyebrow/eyelash alopecia was graded using the 4-point clinician-reported outcome (ClinRO) measure,[6] and beard regrowth was documented as none, partial or complete.

Of 26 patients (17 male; nine female) with a median age of 30 years (range 6–54), 18 had eyebrow AA, four had eyelash AA and nine had beard AA (Table 1). Median duration of facial hair loss was 18 months (range 2–396), while median duration of topical tofacitinib treatment was 8 months (range 3–22). Partial and complete regrowth were observed in four and eight patients with eyebrow AA, respectively. All four patients with eyelash involvement treated with topical ophthalmic tofacitinib experienced complete regrowth. Of those with beard AA, five experienced partial regrowth, while two experienced complete regrowth. Five patients had AA affecting two facial hair-bearing sites (two with eyebrow/beard; three with eyebrow/eyelash). Of those, complete regrowth in both areas was achieved in 80% (four of five) and partial regrowth in 20% (one of five). No adverse events were reported.

Eyebrows, eyelashes and beard play important aesthetic and functional roles. Consequently, loss of facial hair can result in significant psychological impairment. Topical treatments for AA affecting facial hair are currently lacking, given that potent/superpotent topical corticosteroids are contraindicated for prolonged durations and calcineurin inhibitors have failed to demonstrate efficacy.[7] On the other hand, intralesional corticosteroid injections can cause atrophy and may not be tolerated in some cohorts, for example children.

Our study showed that patients with partial eyebrow involvement were more likely to achieve complete regrowth with topical tofacitinib than those with total eyebrow loss. Similarly, complete regrowth was observed in our patients with eyelash alopecia, all of whom had minimal, evenly distributed gaps. However, no such trend was observed in patients with beard AA. In patients with AA affecting more than one facial area, individual hair-bearing sites responded similarly to topical tofacitinib. A similar phenomenon has been described in patients with scalp and beard AA treated