

Letters

RESEARCH LETTER

Long-term Safety of Topical Pimecrolimus and Topical Tacrolimus in Atopic Blepharoconjunctivitis

Atopic blepharoconjunctivitis (ABC) is an ocular manifestation of atopy with a course similar to that of atopic dermatitis: chronic with exacerbations. Topical corticosteroids are widely used for ABC, but long-term use has a well-established risk of adverse effects: increase of intraocular pressure (IOP) or glaucoma, subcapsular cataract, reactivation of herpes simplex virus, and skin atrophy.^{1,2} Some of the adverse effects may manifest in a matter of days in susceptible individuals (IOP increase), while some are relevant in prolonged use (skin atrophy and subcapsular cataract). Topical calcineurin inhibitors pimecrolimus and tacrolimus have shown good long-term safety in the treatment of atopic dermatitis,³ and previous smaller studies of the use of tacrolimus on the eyelids have shown good safety, efficacy, improvement of conjunctival cytology, and a positive effect on IOP.⁴⁻⁶

Methods | We conducted an ethics committee-approved medical record review of ophthalmologist-observed patients with ABC between January 1, 2001, and December 31, 2011, at Helsinki University Skin and Allergy Hospital. Information was collected on topical blepharitis treatments, treatment frequency, conjunctivitis treatments, and follow-up time. Disease characteristics were the severity of symptoms of blepharitis and conjunctivitis, assessed separately on a scale of 0 to 3 (no, marginal, moderate, and severe symptoms) based on the description of symptoms in the medical record. Positive treatment response was defined as a reduced grade of severity. Follow-up started from the induction of topical therapy, and the end point was the last ophthalmologic examination. For the follow-up of malignant neoplasms, the end point was January 31, 2012.

Safety parameters included visual acuity, IOP, corneal and lens status, and data on adverse events. Intraocular pressure was measured with a Goldmann applanation tonometer (Haag-Streit AG). Values of more than 21 mm Hg were considered elevated. A significant rise of IOP was defined as an increase of 6 mm Hg or higher or 20% or more from the baseline (Table 1). Significant use of systemic immunosuppressive medication, concurrent other causes of blepharitis, and other facial dermatoses led to the exclusion of 99 participants.

Results | Of 338 eligible patients, 33 used pimecrolimus, 1%, cream, 297 used tacrolimus ointment (mostly 0.03%) (Table 1), and 8 used topical corticosteroids. The mean follow-up times were 1.5 years for efficacy and 5.7 years (in total, 1945 patient years) for malignant neoplasms (both groups together). No malignant tumors were diagnosed. There were no significant

Table 1. Patient Characteristics and the Use of Concomitant Medication in Pimecrolimus Cream and Tacrolimus Ointment Patient Groups^a

Patient Characteristic/Concomitant Treatment	Pimecrolimus	Tacrolimus
Sex		
Female	21 (63.6)	190 (64.0)
Male	12 (36.4)	107 (36.0)
Age, y		
≤20	4 (9.1)	31 (10.4)
21-40	14 (42.4)	121 (40.7)
41-60	10 (30.3)	123 (41.4)
>60	6 (18.2)	22 (7.4)
Mean, y	41.3	39.1
Follow-up, y		
Clinical, treatment efficacy		
0 to 1	23	195
>1 to 2	4	41
>2	6	61
Mean (range)	1.1 (0.2-6.2)	1.5 (0.1-9.7)
Patient medical records, malignant neoplasms		
0-4	13	81
5-8	16	149
>8	4	67
Mean (range)	5.1 (1.3-10.2)	5.8 (0.2-11.0)
Strength, if applicable, %		
0.1	NA	17 (5.7)
0.03	NA	280 (94.3)
AD outside facial skin		
Yes	19 (57.6)	198 (66.7)
No	13 (39.4)	76 (25.6)
Missing	1 (3.0)	23 (7.7)
Mean use of topical therapy		
Daily or almost daily	12 (36.3)	102 (34.3)
Weekly	15 (45.5)	126 (42.4)
Less than weekly	4 (12.1)	61 (20.5)
Missing	2 (6.1)	8 (2.7)
Mast cell stabilizer eye drops		
Yes	31 (93.9)	272 (91.6)
No	2 (6.1)	25 (8.4)
Antihistamine eye drops		
Yes	1 (3.0)	8 (2.7)
No	31 (97.0)	289 (97.3)
Cyclosporine eye drops		
Yes	4 (12.1)	28 (9.4)
No	29 (87.9)	269 (90.6)
Additional topical corticosteroids		
Yes	7 (21.2)	41 (13.8)
No	26 (78.8)	256 (86.2)

(continued)

Table 1. Patient Characteristics and the Use of Concomitant Medication in Pimecrolimus Cream and Tacrolimus Ointment Patient Groups^a (continued)

Patient Characteristic/Concomitant Treatment	Pimecrolimus	Tacrolimus
Nasal corticosteroids		
Yes	1 (3.0)	24 (8.1)
No	32 (97.0)	273 (91.9)
Inhalation corticosteroids		
Yes	6 (18.2)	65 (21.9)
No	27 (81.8)	232 (78.1)

Abbreviations: AD, atopic dermatitis; NA, not applicable.

^a Data are given as number (percentage) unless otherwise indicated.

changes in visual acuity and no subcapsular cataract or other treatment-related changes in the lens or the cornea observed. Instead, minor disease-related corneal changes reduced 37.5% with pimecrolimus and 34.6% with tacrolimus. The mean IOP decreased 0.5 to 0.6 mm Hg, and the number of patients with elevated IOP decreased 75% to 80% in both groups (eFigure 1 in the Supplement). In a subgroup of patients with elevated IOP at the baseline, the mean IOP decrease was 6.6 mm Hg ($P = .02$) in the tacrolimus group and 6.9 mm Hg ($P = .18$) in the pimecrolimus group (eFigure 2 in the Supplement).

Total discontinuation rates were 56.1% in the pimecrolimus group and 11.0% in the tacrolimus group: 33.3% of pimecrolimus treatments and 9.1% of tacrolimus treatments were discontinued due to patient-reported adverse effects, and lack of treatment response led to discontinuation of 22.8% of started treatments in the pimecrolimus group compared with 1.6% in the tacrolimus group (Table 2).

Treatment response rates for blepharitis were 78.8% with pimecrolimus and 89.9% with tacrolimus ($P = .06$). In multivariable logistic regression analysis of treatment response, adjusted for confounding factors, tacrolimus seemed more efficacious, with odds ratios of 2.37 (95% CI, 0.90-6.22) for blepharitis and 2.34 (95% CI, 1.02-5.40) for conjunctivitis compared with pimecrolimus (eMethods in the Supplement).

Four patients (12.1%) in the pimecrolimus group and 18 (6.1%) in the tacrolimus group had symptoms of ocular or eyelid herpes simplex virus infection during follow-up, but most of these were confirmed reactivations (Table 2). In a subgroup analysis, there were no infections, no significant changes in IOP or visual acuity in the tacrolimus, 0.1%, subgroup, and no significant difference in efficacy between the tacrolimus, 0.03%, and tacrolimus, 0.1%, groups. Only 1 patient (5.9%) discontinued treatment in the tacrolimus, 0.1%, subgroup.

Discussion | In previous studies of topical calcineurin inhibitors for ABC, the numbers of patients have been small and the follow-up times limited to a few months. Knowledge of long-term ocular safety is valuable for physicians prescribing tacrolimus ointment to be used in close proximity to the eye. The discrepancy in group sizes and the retrospective setting are limitations of this study.

We conclude that both topical calcineurin inhibitors show good long-term safety profiles. Tacrolimus ointment seems

Table 2. Adverse Effects and Tolerability in the Pimecrolimus Cream and the Tacrolimus Ointment Patient Groups^a

Characteristic	Pimecrolimus	Tacrolimus
Used as the main treatment for blepharitis, patients, total	33	297
Treatment periods or attempts, total	57	308
Discontinuations due to insufficient response or adverse effects	32 (56.1)	34 (11.0)
Not enough response	13 (22.8)	5 (1.6)
Adverse effects or tolerability	19 (33.3)	28 (9.1)
Not known	0	1 (0.3)
Eyelid or ocular HSV symptoms during follow-up	4 (12.1)	18 (6.0)
Prior history of eyelid or ocular HSV symptoms	4 (12.1)	14 (4.7)
New manifestations of eyelid or ocular HSV	0	4 (1.3)
Other infections during follow-up	0	8 (2.7) ^b
Malignant neoplasms of the eye or eyelid/periorbital skin	0	0
New glaucoma diagnoses during follow-up	0	0
Significant rise of IOP during follow-up ^c	0	1 (0.3) ^d
Elevated IOP at the baseline	3 (9.1)	15 (5.1)
Elevated IOP at the end of follow-up	1 (3.0)	3 (1.0)

Abbreviations: HSV, herpes simplex virus; IOP, intraocular pressure.

^a Data are given as number or number (percentage).

^b Five patients with reported bacterial conjunctivitis, 2 patients with a sporadic eyelid molluscum contagiosum, and 1 patient with bacterial infection of the eyelid skin.

^c An increase of 6 mm Hg or higher in either eye if IOP at the end was 20 mm Hg or higher, or 20% or more rise from the baseline if IOP at the end was elevated.

^d None of these patients had elevated IOP (>21 mm Hg) at the end of follow-up.

more effective and better tolerated on the eyelid than pimecrolimus cream, and it is efficacious in treating both blepharitis and conjunctivitis. It does not increase IOP or cause glaucoma, subcapsular cataract, or atrophy of the skin, and no malignant neoplasms were detected in exposure areas treated by high UV radiation. Additional prospective studies are needed to address the efficacy compared with topical corticosteroids, but based on our experiences and data, tacrolimus ointment is a possible first-line treatment option in the long-term management of ABC.

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Excess Adiposity Preceding Pediatric Psoriasis

As for adult psoriasis, pediatric psoriasis has recently been associated with obesity, increased waist circumference percentiles, and waist-to-height ratios, and metabolic laboratory abnormalities¹⁻³ (eTable in Supplement). Although obesity could theoretically result from the functional limitations and

psychosocial impact of psoriasis, adult females self-reported that obesity developed before psoriasis⁴ and high body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) in adolescent girls preceded psoriasis hospitalization in adults.⁵ To our knowledge, whether obesity precedes pediatric psoriasis or psoriasis leads to childhood obesity has not been addressed. In a pilot study with a new cohort, we addressed the temporal association of pediatric psoriasis and increased adiposity in 27 overweight and obese children with psoriasis.

Methods | See the eMethods in the Supplement. The study was approved by the institutional review board at all centers, and written informed consent was obtained from each participant prior to the study initiation, adhering to the Helsinki Guidelines. The BMI percentiles of overweight (85th ≤ BMI percentile < 95th) and obese (BMI percentile ≥ 95th) children with psoriasis at 3 pediatric dermatology referral centers were determined

at onset of psoriasis, 1 and 2 years before (required for inclusion), and, if available, 1 and 2 years after psoriasis onset.

Results | Of 37 serially examined and enrolled children with psoriasis with excess adiposity, 27 had sufficient data sets from pediatricians to meet inclusion criteria (Table); incomplete data reflected lack of an annual check, transfer of pediatrician, and/or lack of pediatrician cooperation. The mean BMI percentile at enrollment was 96th, with 30% classified as overweight and 70% as obese. Involved body surface area (BSA) was greater in obese children (n = 9 [50%] with a BSA > 20%) than in overweight children (n = 1 [17%] with BSA > 20%) (P = .001). Overall, 25 of 27 patients (93%) were overweight or obese at onset and at 1 and 2 years before onset of psoriasis (Table). One and 2 years after onset, 24 (91.7%) and 22 (100%), respectively, were overweight

Table. Demographic and Clinical Data for 27 Patients

Characteristic	Value
Females, No. (%)	14 (56)
Current age, mean (SD) [range], y	12.9 (3.3) [4-17]
Birth weight, mean (SD) [range], kg	3.4 (0.7) [2.5-5.4]
Disease severity, No. (%)	
Mild disease	13 (48)
Moderate disease	4 (15)
Severe disease	10 (41)
Systemic immunosuppressant use, No. (%)	8 (30)
Phototherapy, No. (%)	4 (15)
Age at onset of psoriasis, mean (SD) [range], y	8.7 (3.1) [2-14]
Age at onset of obesity, mean (SD) [range], y	4.1 (2.3) [2-12]
Duration of psoriasis, mean (SD) [range], y	4.3 (3.1) [0.2-11]
Personal history of psoriasis, No. (%)	
Onset as guttate psoriasis	6 (22)
Psoriatic arthritis	2 (7)
Scalp involvement	23 (89)
Nail involvement	8 (30)
Family history, No. (%)	
Psoriasis	11 (41)
Obesity	13 (48)
Hyperlipidemia	13 (48)
BMI percentile, mean (SD), median (n = 27)	
2 y prior to psoriasis onset	94 (7) [98]
1 y prior to psoriasis onset	94 (9) [98]
At the time of psoriasis onset	95 (6) [99]
BMI percentile, mean (SD), median (n = 25)	
1 y after psoriasis onset	95 (5) [97]
2 y after psoriasis onset	96 (3) [97]
Percentage overweight vs percentage obese, Total (n = 27)	
2 y prior to psoriasis onset	26 vs 67 (93)
1 y prior to psoriasis onset	26 vs 67 (93)
Onset of psoriasis	26 vs 67 (93)
Percentage overweight vs percentage obese, Total (n = 25)	
1 y after onset	33 vs 58 (92)
2 y after onset	23 vs 77 (100)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).