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Tacrolimus 0.1% versus ciclopiroxolamine 1% for maintenance therapy in patients with severe facial seborrheic dermatitis a multicenter, double-blind, randomized controlled study

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70

71 **Introduction**

72

73 Seborrheic dermatitis (SD) is a frequent skin disorder which prevalence has been
74 estimated at between 2.5% and 3% of the general population (1–6). The role of
75 *Malassezia* and an inflammatory reaction characterized by an increase in pro-
76 inflammatory cytokines such as IL2 has been suggested (7–9).

77

78 Some types of SD are considered severe due to their highly recurrent and
79 sometimes chronic course. These severe types of SD have a major impact on
80 patients' quality of life (10). Patients affected by severe SD often chronically use large
81 quantities of topical CS, leading to CS-dependent lesions and CS side effects.

82

83

84 The efficacy of topical anti-fungal drugs has mainly been assessed during the acute
85 phase of SD (11–14). Although these drugs are widely used as maintenance
86 treatment of SD in clinical practice, their efficacy has only been assessed over short
87 periods of time (4 weeks). Moreover, when tested versus placebo in randomized
88 controlled studies, the efficacy of topical anti-fungal drugs was limited, even in
89 moderate types of SD(13,15) .

90

91 Tacrolimus (Protopic®) a calcineurin inhibitor, is a local immunosuppressant
92 which is mainly used in the treatment of atopic dermatitis. Tacrolimus ointment has
93 been demonstrated to be effective in the prevention of flares in patients with atopic
94 dermatitis (16). The efficacy of topical calcineurin inhibitors, tacrolimus and

95 pimecrolimus in the treatment of SD has been suggested in few studies, most of
96 them having included a limited number of patients (17–24).

97
98 The objective of this study was to compare the efficacy and tolerance of 0.1%
99 tacrolimus ointment versus 1% ciclopiroxolamine as maintenance therapy in patients
100 with severe facial SD, after the clearance of SD lesions with an initial topical CS
101 treatment, in order to reduce initial skin inflammation and improve local tolerance. We
102 chose tacrolimus in this study, since pimecrolimus is not available in France.

103

104 **Patients and methods**

105

106 **Participants**

107 Inclusion criteria in the initial open-label phase were the following: i) adult patients
108 aged 18 years and older, ii) diagnosis of severe facial SD. The diagnosis of SD was
109 made clinically on the presence of erythema and / or squamous lesions located on
110 the seborrheic areas of the face (1). Scalp and other extra facial localisations were
111 not taken into account. Severe SD was defined as: i) a clinical severity score ≥ 4 on a
112 scale ranging from 0 to 8, and ii) a chronic or recurrent course characterized by the
113 onset of at least 3 recurrences during the last six-month period, or a continuous or
114 intermittent course of SD with skin lesions which were present for more than 15 days
115 during the last two-month period. The severity of SD was evaluated according to a 1-
116 8 item scale detailed in the Supplementary appendix

117

118 Inclusion criteria in the double-blind maintenance phase was achievement of
119 complete remission (disappearance of erythema and desquamation corresponding to

120 a total score of 0), or almost complete remission (persistence of mild erythema or
121 mild desquamation corresponding to a total score of 1 out of 8), 7 days after the start
122 of treatment with topical desonide.

123 Main exclusion criteria are detailed in the Supplementary Appendix.

124

125 **Procedures**

126 This academic double-blind randomized, controlled trial (RCT) was conducted
127 from January 2014 to April 2017 in 5 Dermatology Departments and by 15 office-
128 based dermatologists from five regions in France. The study included two treatment
129 phases. Patients in the initial open-label phase were treated with desonide 0.05%
130 cream, which was applied twice a day for 7 days. Patients whose lesions were
131 cleared or almost cleared after this initial treatment were included in the double-blind
132 phase, and randomly assigned in a 1:1 ratio to receive twice weekly applications of
133 tacrolimus 0.1% ointment, or twice weekly applications of ciclopiroxolamine 1%
134 cream until their first relapse or for up to 24 weeks in patients who did not relapse.
135 Treatment was assigned through central computer-generated randomization. All
136 participants remained unaware of group assignments once the decision was made to
137 stop enrollment.

138

139 **Study assessments and treatment of relapses**

140 The total duration of the study was 25 weeks. Four visits were planned: 1)
141 inclusion visit at Day 1; 2) randomization visit which was scheduled at Day 7 (end of
142 the open-label phase of the study); Patients who were in complete or almost
143 complete remission were given the study products for the maintenance phase
144 (tacrolimus or ciclopiroxolamine) at the end of this visit 3) patients who relapsed

145 during the double-blind maintenance phase had to call investigators to plan an
146 additional visit within 2 days after the phone call for assessment of the primary
147 endpoint; 4) end of study visit at Day 180. Additionally, three phone call assessments
148 were performed at Days 30, 90 and 120 to evaluate treatment tolerance and
149 compliance.

150 Treatment of relapsing patients is detailed in the Supplementary Appendix

151

152 **Outcome measures**

153 The primary endpoint was Disease-Free Duration (DFD) defined as the time
154 from randomization to first relapse, i.e., the duration during which patients remained
155 completely cleared (disappearance of erythema and desquamation corresponding to
156 a total score of 0), or almost completely cleared (persistence of mild erythema or mild
157 desquamation, corresponding to a total score of 1 out of 8).

158 The first relapse had to be confirmed by the investigator during an additional visit,
159 which was performed within 48 hours after the telephone call of patients who
160 suspected a relapse. Relapse was defined as the recurrence of erythema or
161 desquamation on the seborrheic areas of the face with a total score ≥ 3 .

162 Secondary endpoints were: i) number of relapses during the double-blind phase
163 of the study, ii) cumulative number of days with SD lesions according to patients'
164 evaluation, iii) cumulative number of days during which patients had to apply
165 desonide cream to treat relapsing SD lesions during the double-blind phase of the
166 study, iv) evolution of the quality of life and stress level during the study, as
167 evaluated by the French version of Skindex and Dermatology Life Quality Index
168 (DLQI) questionnaires, (25–27) and Cohen PSS 14 stress scale (28,29), respectively

169 v) safety evaluated by severe and non-severe treatment-related side effects, vi)
170 patients' global assessment of drug efficacy and tolerance.

171 Compliance was evaluated according to forms filled in by the patients during the
172 study and the number of tubes of study products used.

173

174 **Statistical analysis**

175 We hypothesized that the median DFD of patients would increase from 8 weeks in
176 patients treated with ciclopiroxolamine to 12 weeks in those treated with tacrolimus
177 (150% increase in the DFD)(17,18). To achieve 80% power relative to this difference
178 at the two-sided 0.05 level and allowing for 10% dropouts, 240 patients (2x120) were
179 required for enrolment in the initial open phase. Expecting that 90% of patients would
180 be cleared or almost cleared after the initial CS treatment, 260 patients (2x130) had
181 to be randomized in the double-blind phase of the study. Analyses were based on the
182 intention-to-treat principle.

183 The distribution of the primary endpoint (DFD, i.e., number of days without
184 lesions from the start of the double-blind phase of the study to the visit at which the
185 first relapse was confirmed by the investigator) was estimated from Kaplan-Meier's
186 method and comparisons between the two treatment groups relied on the log-rank
187 test.

188 Multivariate Cox regression analysis was performed to control for several potential
189 baseline prognostic factors on DFD (i.e., gender, baseline severity of lesions,
190 inflammatory or squamous type of SD, stress level assessed by the Cohen PSS 14
191 stress scale (0-20, 21-26 and ≥ 27), and DLQI and Skindex scores. We estimated
192 Hazard Ratios (HR) and corresponding 95% Confidence Intervals (CI) from Cox
193 regression.

194

195 Statistical analyses used for secondary endpoints, study oversight and role of the
196 funding source are detailed in the Supplemental Appendix.

197

198 **Results**

199 **Population of the study**

200 Between January 2014, and April 2017, 114 patients of mean age 46.2 ± 15 years
201 were included. Baseline characteristics of patients recruited in Dermatology
202 Departments and by office based dermatologists are shown in the Supplementary
203 Appendix. All 114 patients were cleared or almost cleared after the open phase of
204 CS treatment, and were randomly assigned to receive either tacrolimus (57 patients)
205 or ciclopiroxolamine (57 patients) in the double-blind phase of the trial. Owing to slow
206 patient accrual, enrollment was stopped before the target sample size was reached.

207 Fifteen patients did not complete the study, 6 in the tacrolimus group and 9 in the
208 ciclopiroxolamine group. Reasons for drop-out are detailed in Figure 1. The two
209 groups were well-balanced for main baseline characteristics, except DLQI and
210 Skindex scores which were higher in patients from the tacrolimus group (Table 1).

211

212 **Primary outcome**

213 Twelve out of 57 patients (21.1%) had at least one relapse in the tacrolimus group
214 versus 23 patients (40.4%) in the ciclopiroxolamine group. Median delay to first
215 relapse was 91.5 days [15-195] in the tacrolimus group versus 27 days [13-201] in
216 the ciclopiroxolamine group.

217 Patients in the tacrolimus group had longer DFD than patients in the
218 ciclopiroxolamine group ($p=0.018$) (Figure 2). This difference corresponded to a

219 hazard ratio (HR) of relapse of 0.44 (95% CI [0.22-0.89], $p=0.022$, from Cox
220 proportional hazard model). After adjusting for gender, SD type (squamous versus
221 inflammatory or mixed), baseline severity, Cohen's PSS, DLQI and Skindex scores,
222 the beneficial effect of tacrolimus was still evidenced with a hazard ratio (HR) of
223 relapse of 0.32 (95% CI [0.13-0.80], $p=0.015$).

224

225 We then performed a sensitivity analysis, in which all patients who prematurely
226 withdrew from the study (patients who were lost to follow-up, moved, experienced
227 treatment adverse event, withdrew their consent) were considered as treatment
228 failure for the primary endpoint from the time of their last visit. Patients in the
229 tacrolimus group still had longer DFD than patients in the ciclopiroxolamine group
230 ($p=0.008$), corresponding to a hazard ratio (HR) of relapse of 0.47 (95% CI [0.26-
231 0.83], $p=0.010$).

232

233 **Secondary Outcomes**

234 A total number of 36 relapses were observed in patients from the tacrolimus group
235 and 47 relapses occurred in patients from the ciclopiroxolamine group. In order to
236 assess if seasonality could be a confounding factor of relapse, we analyzed the
237 number of patients included or who relapsed according to seasons (Table 2). No
238 difference in the rate of inclusions or relapses was evidenced between the two
239 treatment groups.

240 According to patients' evaluation, the mean cumulative number of days with SD
241 lesions in the ciclopiroxolamine group was 31.6 ± 45.8 days versus 24.4 ± 37.4 days
242 in the tacrolimus group, ($p=0.74$). The mean cumulative number of days during which
243 patients had to apply desonide cream to treat relapsing SD lesions during the double-

244 blind phase of the study was 15.9 ± 13.0 days in the ciclopiroxolamine group versus
245 16.8 ± 14.5 days in the tacrolimus group ($p=0.77$).

246 Two severe adverse events unrelated to study treatments were observed (infectious
247 colitis, flare of Crohn's disease). Thirty-seven treatment-related adverse events were
248 observed in 21 patients from the ciclopiroxolamine group, and 62 adverse events in
249 33 patients from the tacrolimus group, corresponding to a mean number of 0.6 ± 0.9
250 treatment-related adverse events per patient in the ciclopiroxolamine group and $1.1 \pm$
251 1.1 in the tacrolimus group ($p=0.027$). Most frequent adverse events were burning
252 sensation, pruritus and erythema (Table 3). Forty-seven of the 62 (76%) tacrolimus-
253 related adverse events and 37 of the 37 (100%) ciclopiroxolamine-related adverse
254 events were observed in patients with inflammatory/mixed type SD. No cutaneous
255 carcinoma or lymphoma was observed during the study.

256

257 **Patients' Reported Outcomes**

258 Mean improvement in quality of life scores from baseline to the end of the study was
259 -1.4 ± 3.7 points in the ciclopiroxolamine group versus -4.2 ± 4.6 points in the
260 tacrolimus group for the DLQI score ($p=0.11$), and -12.1 ± 18.3 points in the
261 ciclopiroxolamine group versus -22.5 ± 22.9 points in the tacrolimus group for the
262 Skindex score ($p=0.22$).

263 The mean baseline PSS scores of patients in the ciclopiroxolamine and tacrolimus
264 groups were 31.1 ± 6.1 points and 30.9 ± 8.3 out of 50 points respectively, indicating
265 a high level of stress. No significant evolution of this score was observed during the
266 study in either treatment group.

267 Patients' global assessment of the efficacy and tolerance of the study drug was
268 available in 89 cases. Tacrolimus and ciclopiroxolamine were evaluated highly

269 effective by 32 (66.7%) and 20 (48.8%) patients, rather effective by 12 (25.0%) and
270 11 (26.8%) patients, and poorly effective/ineffective by 4 (8.3%) and 10 (24.4%)
271 patients, respectively. Tacrolimus and ciclopiroxolamine were evaluated well
272 tolerated by 28 (58.3%) and 35 (85.4%) patients, rather well tolerated by 14 (29.2%)
273 and 4 (9.7%) patients, and poorly tolerated by 6 (12.5%) and 2 (4.9%) patients

274

275 **Discussion**

276

277 This clinical trial showed that tacrolimus 0.1% ointment applied twice weekly is more
278 effective than ciclopiroxolamine 1% cream for maintenance therapy in patients with
279 severe facial SD. Ciclopiroxolamine was preferred over vehicle as the comparator in
280 this RCT, since although ciclopiroxolamine has been tested as maintenance therapy
281 only on short duration periods, there is extensive clinical experience from practicing
282 dermatologists suggesting its efficacy in chronic types of SD (11,12).

283 Patients assigned to the tacrolimus group had almost twice fewer relapses than
284 those in the ciclopiroxolamine group (12 versus 23 relapses). Additionally, the
285 median delay to first relapse was three-fold longer (91.5 days) in the tacrolimus
286 group than in the ciclopiroxolamine group (27 days), resulting in a highly significant
287 difference in DFD between the two drugs ($p=0.018$). The therapeutic effect of
288 tacrolimus was major since it corresponded to a HR of relapse of 0.44 relative to
289 ciclopiroxolamine ($p=0.022$). Additionally, the beneficial effect of tacrolimus was still
290 evidenced, and even slightly enhanced after adjusting for gender, baseline severity,
291 inflammatory versus squamous type of SD, PSS and quality of life scores (HR of
292 relapse = 0.32; $p=0.015$), the last three variables showing some imbalance between
293 the two groups.

294 No severe drug-related adverse events were observed in this study, in particular no
295 case of cutaneous lymphoma (30,31). As expected, the most frequent side effects
296 were pruritus, burning sensation and erythema, which were more frequently
297 observed in patients with inflammatory/mixed type SD than in patients with
298 squamous type SD. Despite initial applications of desonide cream for 7 days to clear
299 inflammatory lesions, local adverse reactions were quite frequently observed, in
300 particular in patients from the tacrolimus group (1.1 ± 1.1 treatment-related adverse
301 event per patient versus 0.6 ± 0.9 in the ciclopiroxolamine group). Accordingly,
302 patients reported that ciclopiroxolamine tolerance was better than that of tacrolimus.

303

304 Main limitation of our study is that owing to slow patient accrual, enrollment was
305 stopped before the sample size was reached. The final sample of 114 patients was
306 sufficient to provide 80% power to detect a between-group 50% increase of the DFD
307 if the median DFD in the ciclopiroxolamine group was 50% shorter than the
308 hypothesized 8 weeks. Accordingly, a statistically significant difference was obtained
309 for assessment of the primary endpoint (delay to first relapse), since the observed
310 delay to first relapse in patients from the ciclopiroxolamine group (27 days) was in
311 fact 50% shorter than planned in our study hypothesis (8 weeks). Since sunlight has
312 a notable beneficial effect on SD activity, we assessed whether seasonality of
313 inclusion or relapses might be a confounding factor. No difference in that rate of
314 inclusions or relapses was evidenced between the two treatment groups.

315

316 Overall, this academic double-blind RCT has shown that tacrolimus applied twice a
317 week as maintenance therapy after an initial CS treatment with desonide cream is

318 more effective than ciclopiroxolamine to prevent the occurrence of relapse in patients
319 with severe SD.

320

321

322

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327

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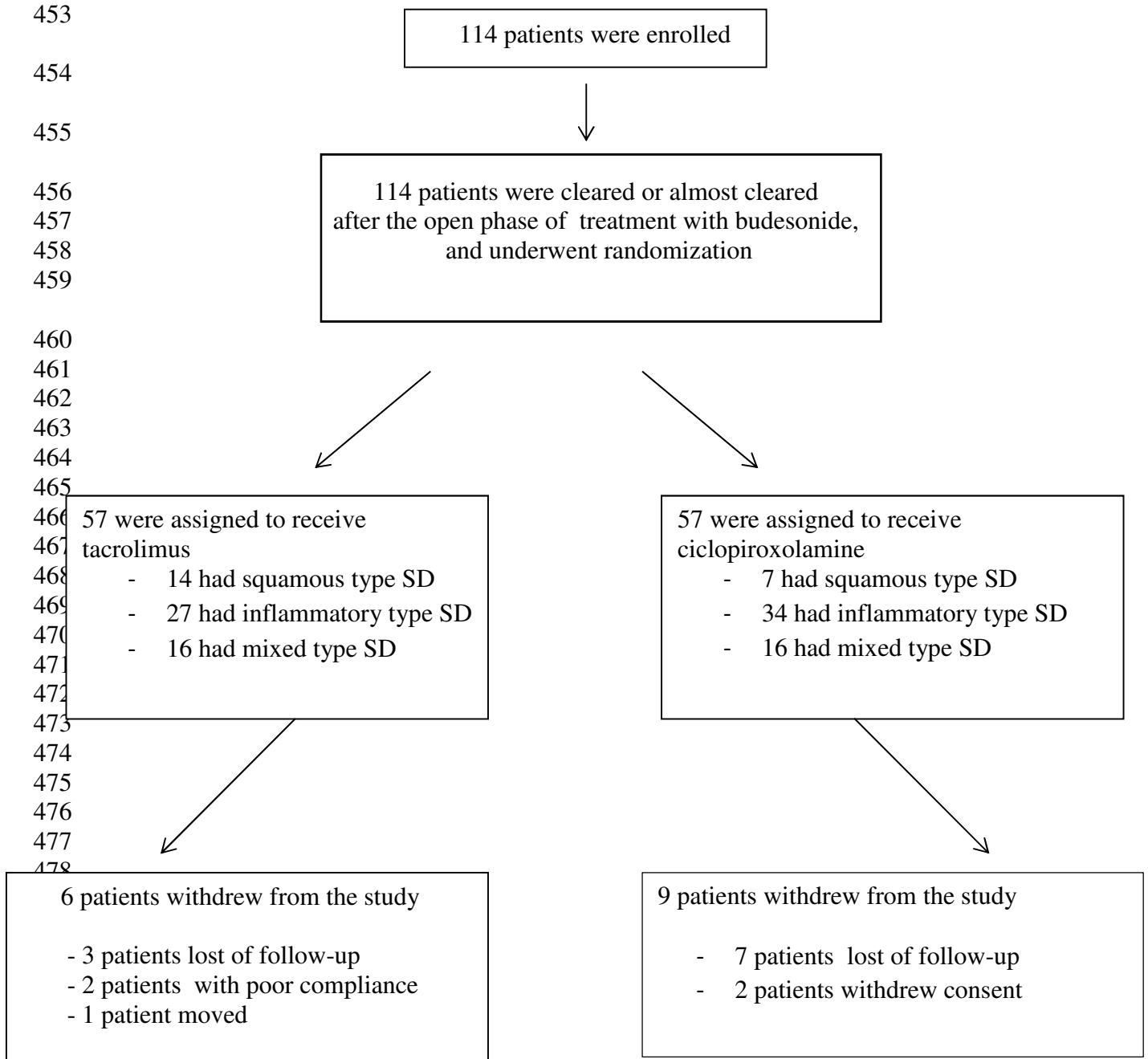
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Legends to Figures

Fig 1. Flow chart of the study

Fig 2. Kaplan Meier Disease Free Duration curves of patients treated with tacrolimus (yellow curve) and ciclopiroxolamine (blue curve)

Figure 1



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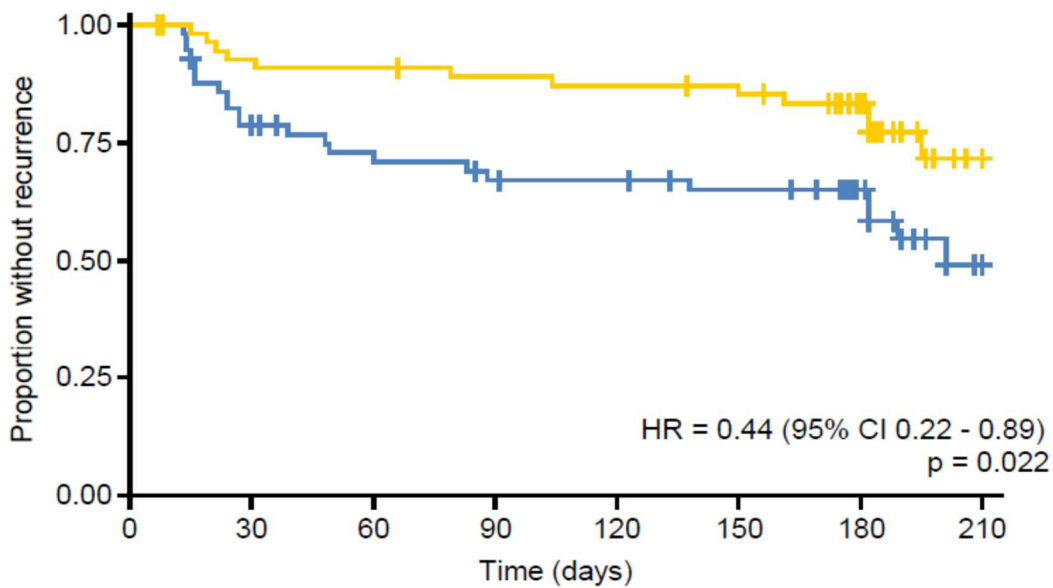
57 patients were analyzed for the primary endpoint
 Patients who dropped out of the study while still in complete remission were analyzed as being in complete remission until the time of the last visit they completed

57 patients were analyzed for the primary endpoint
 Patients who dropped out of the study while still in complete remission were analyzed as being in complete remission until the time of the last visit they completed

490 Figure 2

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No. at risk

—	57	44	38	34	33	30	22	7
—	57	51	50	48	47	46	35	8

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Tables

517 Table 1: Baseline characteristics of study patients according to treatment groups
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	Ciclopiroxolamine (n = 57)	Tacrolimus (n = 57)	P value
Age (years)			
Mean ± SD	47.9 ± 14.7	44.6 ± 15.3	0.2425
Gender			
Female n (%)	12 (21.1)	10 (17.5)	0.635
Male n (%)	45 (78.9)	47 (82.5)	
Severity score			
Mean ± SD	5.3 ± 0.9	5.7 ± 1.3	0.0907
Type of seborrheic dermatitis			
inflammatory n (%)	34 (60)	27 (47)	0.02084
squamous n (%)	7 (12)	14 (25)	
mixed n (%)	16 (28)	16 (28)	
Duration of lesions before inclusion (months)			
Median [range]	86.2 [0 ; 185.3]	49.7 [0 ; 368.7]	0.5073
Cohen's Perceived Stress Scale score			
Mean [SD]	31.1 [6.1]	30.9 [8.3]	0.08674
Skindex score			
Mean [SD]	60.4 [21.4]*	71.1 [24.4]**	0.0101
Dermatology Life Quality Index score			
Mean [SD]	3.77 [3.6]°	6.3 [5.7]°°	0.0089

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521
 522 * on 55 patients
 523 ** on 55 patients
 524 ° on 56 patients
 525 °° on 56 patients

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532 Table 2: Number of inclusions and relapses patients according to seasons

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	Ciclopiroxolamine (n = 57)	Tacrolimus (n = 57)	Total (n = 114)	P *
	n (%)	n (%)	n (%)	
Number of inclusions				0.7931
Winter**	22 (39)	24 (42)	46 (40)	
Spring**	15 (26)	12 (21)	27 (24)	
Summer**	10 (17.5)	8 (14)	18 (16)	
Autumn**	10 (17.5)	13 (23)	23 (20)	
Number of first relapses	n = 23	n = 12	n = 35	0.9577
Winter**	5 (22)	2 (16.5)	7 (20)	
Spring**	11 (48)	5 (42)	16 (46)	
Summer**	4 (17)	3 (25)	7 (20)	
Autumn**	3 (13)	2 (16.5)	5 (14)	

534 * the chi-square test was used for comparison of inclusions and Fisher Exact test for
 535 comparison of relapses
 536 ** The four seasons were determined according to the dates of the solstices. Winter: from Dec
 537 21 to March 19, Spring from March 20 to June 19, Summer from June 21 to September 20
 538 and Autumn from September 21 to December 20.

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Table 3: Number of treatment-related adverse events

	CICLOPIROXOLAMINE	TACROLIMUS
Nature of treatment-related adverse events	n = 37	n = 62
Pruritus	18	23
Burning sensation	17	29 *
Erythema	0	3
Others	2**	7 ***

* including one patient with rosacea

** folliculitis (n=1), herpes (n=1)

*** folliculitis (n=4), herpes (n=2), conjunctivitis (n=1)