ORIGINAL ARTICLE

Outcome and long-term treatment protocol for topical tacrolimus in oral lichen planus

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Abstract

Background and objective Topical tacrolimus has been shown to be beneficial in the treatment of oral lichen planus (OLP). However, long-term effects and its optimal application protocol with gradual reduction have not been studied. Accordingly, we analysed the clinical response of OLP to tacrolimus in our daily clinical practice with a focus on the optimal long-term therapeutic scheme.

Methods Retrospective analysis of all consecutive patients diagnosed with OLP and treated with topical tacrolimus (0.03% oral rinse) in a clinical setting between 2015 and 2020. The objective clinical response was measured by a 4-point scale (complete remission, major remission, partial remission and no response), and subjective impairment by a 3-point scale (severe, moderate and none).

Results Fifty-seven patients (74% women; median age: 66 years) were included. Fifty-six (98%) patients had prior treatment with topical steroids. After introduction of tacrolimus, objective remission (major or complete) was reached by 28%, 62%, 87% and 97% of patients after 3, 6, 12 and 24 months respectively. Subjective remission was reported by 16%, 48%, 69% and 83% after 3, 6, 12 and 24 months of treatment respectively. The treatment frequency could be gradually reduced from initially twice daily to once daily or less in 28%, 61%, 78% and 87% after 3, 6, 12 and 24 months respectively; 41% of patients completely suspended the treatment at one point, but 67% of them experienced a relapse after a median time of 3.3 months. Four patients (7%) developed a squamous cell carcinoma (SCC) during the observation period. Otherwise, there were only few and minor side-effects.

Conclusion Topical tacrolimus can be an effective second-line therapy for OLP refractory to potent topical corticosteroids. The therapy frequency can often be reduced during the maintenance period. Both signs of clinical activity and subjective impairment should guide therapy. Regular follow-up is necessary to recognize possible SCC.

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Conflicts of interest

None declared.

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Introduction

Lichen planus is a mucocutaneous inflammatory disease involving mainly the skin and the oral mucosa. Other mucosae (genital, oesophageal, conjunctival), hair follicles and nails can also be affected.[1–3] Oral lichen planus (OLP) shows a female predominance and an overall prevalence between 1% and 2%.[4]

While the most frequent reticular form of OLP is mostly asymptomatic and does not require treatment, the erosive form is often associated with disabling pain resulting in a substantially reduced quality of life, malnutrition and weight loss.[1–3,5] Since effective therapeutic options are limited, the management of OLP remains challenging.[6–9] First-line treatment of OLP consists of topical corticosteroids. In patients with a refractory course, topical calcineurin-inhibitors like tacrolimus, pimecrolimus and cyclosporine are recommended.[6–9] The beneficial effect of topical tacrolimus has been demonstrated in numerous previous studies.[10–20] However, the follow-up was too short to evaluate the long-term outcome. Specifically, the impact of a gradual reduction of the application frequency and treatment cessation have not been investigated.

We therefore analysed the clinical response of OLP to tacrolimus in daily clinical practice with a focus on the optimal

therapeutic application scheme and possible reduction over time as well as adverse reactions including malignant transformation.

Methods

This study includes all 57 consecutive patients of the Department of Dermatology at the University Hospital of Bern and the Department of Oral Surgery and Stomatology (in a joint consultation of LF and VS) diagnosed with OLP according to the clinical and histopathological criteria of the WHO[21] and treated with topical tacrolimus between 01 January 2015 and 01 October 2020 after treatment failure under potent topical corticosteroids. The patients were instructed to perform a 5-min mouthwash with a magistral preparation of 0.03% tacrolimus solution (solution: sodium carboxymethylcellulose 1%, methyl parahydroxybenzoate 0.07%, propyl parahydroxybenzoate 0.03%, distilled water 98.9%).

The clinical OLP subtype was classified as either only hyperkeratotic (all non-erosive subforms), both erosive/hyperkeratotic or only erosive. Clinical remission was evaluated using the following 4-point scale: CR (complete remission): regression of all visible oral lesions; MR (major remission): regression of >50% of the lesions; PR (partial remission): regression of 25–50% of the lesions; no response (<25% regression). In addition, subjective impairment was assessed using a 3-point scale: severe (compromised food intake), moderate or no impairment. Further evaluated parameters were adjustments of the therapy regimen at every follow-up, adjuvant treatment, malignant transformation and adverse drug reactions.

Statistical analysis

For descriptive purposes, continuous data were presented as medians with ranges, while categorical data were reported as absolute numbers with percentages. A discrete longitudinal analysis was performed by categorizing available visits around predefined time points: 0 (baseline), 3, 6, 9, 12, 24, 36, 48 and 60 months. More specifically, the first closest visit around each time point was retained in the discrete analysis. Patients without an available visit within the interval considered were not included in this analysis. Tests for linear trend of different outcomes changes across visits were performed using generalized estimating equations (GEEs) with binomial or multinomial distributions, assuming an exchangeable correlation structure.

The Kaplan–Meier estimator was used to calculate cumulative probabilities for the incidence of specific outcomes at follow-up. Incidence estimates were calculated along with their 95% confidence intervals (CI). The median times to the first event were computed as well and presented with their 95% CI.

Cohen's kappa was used to compute the degree of concordance between objective vs. subjective improvement at follow-up and presented with its 95% CI. All tests were considered statistically significant at P-value <0.05. Analyses were carried out with SPSS software v.26 (IBM Corp, Armonk, NY, US).

Results

Clinical characteristics

The demographic and clinical characteristics of the enrolled patients are presented in Table 1. Fifty-seven patients were included, 42 women and 15 men (ratio M: F = 1: 2.8) with a median age at baseline of 66 years (range: 33–90 years). Forty-six (80.7%) patients showed a combination of hyperkeratotic and erosive lesions of OLP, 7 (12.3%) only hyperkeratotic and 4 (7%) only erosive lesions. The buccal mucosa was the most commonly affected intraoral localization in 52 (91.2%), followed by the gingiva in 42 (73.7%) cases, but the majority showed multiple affected sites. An extraoral involvement was documented in 15 patients (26.3%).

Before the initiation of tacrolimus, 56 patients (98.2%) were treated with potent topical steroids – either betamethasone mouth rinse (betamethasone dihydrogenphosphate-disodium water-soluble tablets 0.5 mg, commercially available, in 1 dL water) or fluocinonide gel 0.05%, commercially available. Systemic corticosteroids and doxycycline were concomitantly given in three (5.3%) and one (1.8%) patients respectively. One

Table 1 Clinical characteristics of patients included in the study (N = 57)

		N = 57	%
Sex	Female	42	73.7
	Male	15	26.3
Age at therapy start	Median, years (Range; IQR)	66 (33–90; 55–75)	
Predominant form	Only hyperkeratotic	7	12.3
	Hyperkeratotic/ erosive	46	80.7
	Only erosive	4	7.0
Localization†	Buccal mucosa	52	91.2
	Gingiva	42	73.7
	Tongue	22	38.6
	Lips	9	15.8
	Palate	7	12.3
Extraoral involvement†	None	42	73.7
	Genital	9	15.8
	Cutaneous	8	14.0
	Hair follicles	1	1.8
	Oesophageal	1	1.8
Previous therapy†	None	1	1.8
	Topical steroids	55	96.5
	Systemic steroids	3	5.3
	Doxycycline	1	1.8
Duration of prior therapy	Median, months (Range; IQR)	4.0 (1.0–168.0; 2.0–6.0)	
Length of follow-up	Median, months (Range; IQR)	19.6 (2.1–66.5; 8.5–33.2)	
Malignant transformation		4	7.0

†Multiple locations/involvements/therapies were possible.
IQR, interquartile range.

patient (1.8%) was given tacrolimus as first-line. The median duration of the prior therapy was 4 months (range: 1 month to 14 years). The median follow-up duration was 19.6 months, ranging from 2.1 to 66.5 months.

Clinical response to treatment

The objective therapeutic response to topical tacrolimus is visualized in Fig. 1 and Table S1. Clinical remission was evaluated after 3, 6, 9, 12, 24, 36 and 60 months. Four patients (7.0%) were lost to follow-up in the first 3 months. After 3 months of treatment the cumulative number of patients who reached objective remission (CR or MR) was 16 (estimated cumulative incidence: 28.4%; 95% CI: 16.6–40.2), 33 (62.2%; 95% CI: 48.9–75.5) after 6 months, 44 (88.3%; 95% CI: 78.3–98.3) after 12 and 47 (97.1; 95% CI: 91.6–100) after 24 months. The median time to first objective remission was 4.4 months (95% CI: 3.3–5.5).

Complete remission was seen in no patient at month 3, in three patients (cumulative incidence 6%; 95% CI: 0–12.8) at month 6, four patients (8.5%; 95% CI: 0.5–16.5) at month 12 and five patients (11.7%; 95% CI: 1.9–21.5) at month 24.

Among the 49 patients who reached objective remission at some point during the study period, the cumulative number of clinical relapses (any objective decline after initial improvement >50%) was 7 (cumulative incidence: 16.5%; 95% CI: 5.3–27.7) at month 6, 12 (30.4%; 95% CI: 15.9–44.9) at month 12 and 15 (41.3%; 95% CI: 24.4–58.2) at month 24. The median time to relapse after reaching objective remission was 27.2 months (95% CI: 17.1–37.4).

Subjective improvement

The subjective therapeutic response is presented in Figure 2 and Table S1. Overall, 56 of 57 (98.2%) patients reported an initial improvement on tacrolimus. Before initiation of therapy, 42 patients (73.7%) reported a severe impairment with compromised food intake. Ten patients (17.5%) had moderate symptoms, while 5 (8.8%) specified no subjective impairment. After 3 months the cumulative number of patients reaching subjective remission (no impairment) was 9 (cumulative incidence: 15.9%; 95% CI: 6.3–25.5), 26 (48.0%; 95% CI: 34.7–61.3) after 6 months, 37 (70.9%; 95% CI: 58.2–83.6) after 12 and 42 (84.9%; 95% CI: 73.7–96.1) after 24 months. The median time to first subjective remission was 6.3 months (95% CI: 4.4–8.2).

Comparing the two parameters of objective and subjective remission, Cohen's kappa was 0.42 (95% CI: 0.33–0.51), representing an only moderate agreement.

Adaptation of treatment frequency

The initial dosage of the tacrolimus oral rinse was twice daily for 5 min. Two patients (3.5%) started with three times daily and six patients (10.5%) with once daily. In case of an objective clinical remission and impairment reduction, the treatment frequency was gradually reduced. The respective percentages of the frequencies at each cut off point are displayed in Figure 3 and Table S2. After 3 months, 28.4% of the patients were able to use the oral rinse once daily or less, after 6 months 60.5%, after 12 months 77.5% and after 24 months 86.7%. Cases with a clinical relapse were managed by a re-increase of application frequency.

The cumulative number of patients who once completely suspended the treatment during the evaluated time period was 17

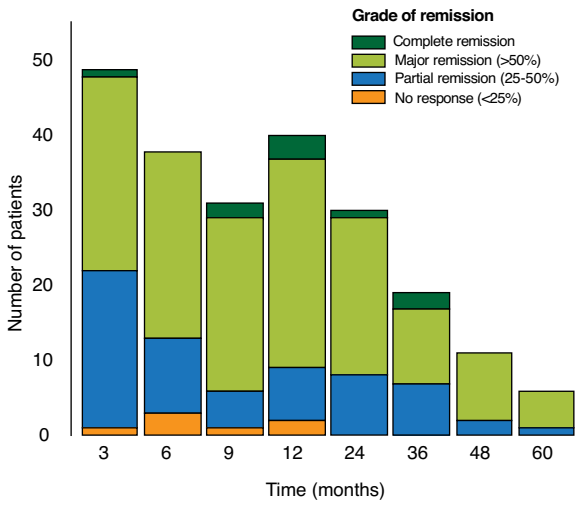

Figure 1 Grade of remission at follow-up.

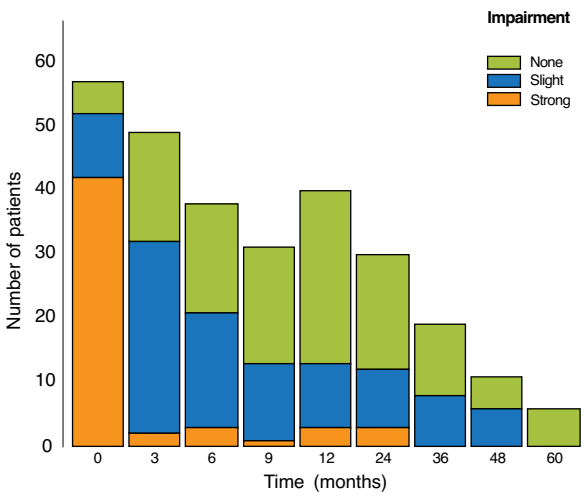

Figure 2 Judge on impairment at follow-up.

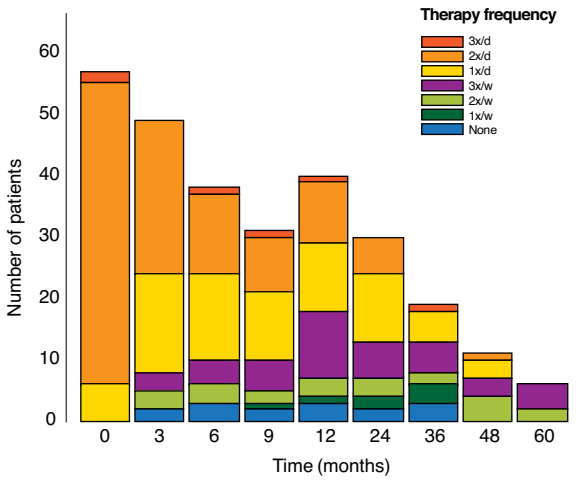

Figure 3 Therapy frequency at baseline and follow-up.

(cumulative incidence: 41.2%; 95% CI: 24.7–57.7). Among these, 12 patients continued to be followed-up and seven patients (estimated cumulative incidence: 75.1%; 95% CI: 45.9–100) restarted the treatment after a median time of 3.2 months (95% CI: 2.3–4.1) because of a recrudescence of clinical signs.

Adjuvant treatment

Because of an insufficient disease control on topical tacrolimus, treatment escalation was necessary in seven cases (12.3%), which were excluded from the final analysis after this point. Five patients (8.7%) received additional systemic corticosteroids, two of them in combination with topical retinoids, while the other two patients were given methotrexate.

Side-effects

A total of five patients (8.7%) reported side-effects: two patients (3.5%) had a burning sensation, two (3.5%) presented with dysgeusia, while one (1.8%) had nausea. Except for the latter case which resulted in discontinuation of therapy, there was no interference with the treatment protocol.

Malignant transformation

During the whole observation period of this study, four patients (7%) were diagnosed with a squamous cell carcinoma (SCC) of the oral mucosa. They were two women and two men with a median age of 80 years (range: 59–82 years). Characteristics and treatment are presented in Table 2. All were diagnosed in an early stage (pTis, pT1). One patient (Table 2, Nr. 4) had a history of SCC on the tongue 4 years before initiation of tacrolimus, while another (Table 2, Nr. 1) was diagnosed with two simultaneous SCC in different localizations during the study period. The median duration of tacrolimus use was 20.5 months (range: 1–36 months) until diagnosis of the oral SCC; in one patient (Table 2, Nr. 2) – with 30 pack years – this was only 1 month. Three patients continued with tacrolimus after the oncological-surgical intervention while one stopped.

Loss to follow-up

The cumulative number of patients lost to follow-up was 19 patients (cumulative incidence: 33.3%; 95% CI: 21.1–45.5) after 12 months; 32 (56.1%; 95% CI: 43.2–69.0) after 24 months; 44 (77.2%; 95% CI: 66.2–88.2) after 36 months; 49 (86.0%; 95% CI: 77.0–95.0) after 48 months; and 52 (91.2%; 95% CI: 83.9–98.5) after 60 months.

Discussion

The treatment of OLP can be challenging for both affected patients and treating physicians. An effective therapy is essential for pain relief, improvement of quality of life as well as risk reduction for malignant transformation. If potent or super-potent topical corticosteroids as first-line treatment do not entail a sufficient improvement, the calcineurin inhibitor tacrolimus can be a valuable and effective alternative to treat OLP.[10–20,22,23]

The efficacy of topical calcineurin inhibitors in comparison to topical corticosteroids has been examined in four conventional

Table 2 Clinical characteristics of the four patients with an oral squamous cell carcinoma (SCC)

Patient	Sex	Age (years)	Smoking	Stage of SCC	Intraoral localization of SCC	Duration in month of Tacrolimus application	Treatment of SCC
1	F	82	Never	pT1 cN0 cMo pT1 cN0 cMo	– Gingiva – Palate	24	Tumour resection Neck dissection
2	M	59	Former (30 py)	pT1 cN0 cMo	Tongue border	1	Tumour resection Neck dissection Radiotherapy
3	M	80	Never	pTis cN0 cMo	Oral vestibule	17	Resection
4	F	70	Former (1 py)	pT1 cN0 cMo pTis†	– Gingiva – Tongue border	36	Resection

†History of pTis 4 years before initiation of tacrolimus.
c, clinical; F, female; M, male; M, metastasis (distant); M0, none; N, node; N0, none; N1, ipsilateral <3 cm; p, post therapeutic; py, pack years; T, Tumour size; T1, <2 cm; T2, 2–4 cm; Tis, *in situ*.

meta-analyses. While three studies concluded that both therapies are similarly effective,[17,18,24] one report indicated that topical tacrolimus is superior compared to topical steroids.[16] In a meta-analysis of multiple interventions, tacrolimus showed the best clinical response and the best symptom-reducing effect when compared to placebo and other topical interventions, while dexamethasone had the best sign-reducing effect and showed the least adverse events.[19] However, the overall evidence is of low level and the most recent Cochrane review concluded that although topical tacrolimus may be more effective in terms of subjective pain relief, the differences concerning objective clinical response and adverse effects were uncertain and partially conflicting.[25]

In our department, the use of topical tacrolimus as second-line treatment for OLP has been conducted for more than a decade as well as clinically evaluated.[13] Consequently, our follow-up with 66.5 months (median 19.6 months) is longer than all previously published studies regarding OLP treatment with tacrolimus. The 0.03% oral mouthwash formulation was used based on our previously observed beneficial results.[13] The latter implied sufficient local bioavailability with a positive effect on the mucosal inflammatory process. The utilized 0.03% concentration further minimized the risk of systemic absorption. Finally, the oral mouthwash was preferred to the commercial 0.03% or 0.1% tacrolimus ointment by the patients because of its much easier use and better subjective tolerability with less irritation and burning sensation.

Compared to other studies, the clinical characteristics of the patients included in our study were congruent, with a female predilection and a median age in the sixth decade.[2,4,7] Erosive lesions were found in 87.7% which is similar to other studies who included only recalcitrant symptomatic OLP patients,[12,13,20,26] but significantly higher than the overall OLP population, in which 32.5% of cases show an erosive variant.[4] Both the objective and subjective remission showed no significant association with any baseline parameter as sex, age, OLP subtype, localization, prior treatments or their duration.

Since complete remission (CR) was defined as a complete absence of visible lesions, only very few patients met this condition due to persistent reticular alterations of the oral mucosa. Most patients belong therefore to the major remission (MR) group, with a positive therapy response and no remaining erosions. Consequently, our CR rate of 0% at month 3, 6.1% at month 6 and 8.5% at month 12 is significantly lower than in most previous studies with reported CR rates ranging from 14% up to 59.5%.[12,13,20,26] However, by pooling both CR and MR as clinical remission with no erosive lesions, we observed clinical remission in 28.4% after 3 months, 62.2% after 6 months and 88.3% after 12 months of treatment.

A similar retrospective analysis of topical tacrolimus in OLP was pursued in four other previous studies: One study of 13 patients using either 0.03% mouthwash or 0.1%/0.3% ointment found complete remission in 23% and partial response and 62% after 8 weeks.[27] Another study with 37 patients receiving either 0.03% or 0.1% ointment described 84% partial to complete response after 6 months, whereas in another report 91.3% of 23 patients using 0.1% ointment achieved clinical improvement after 6 weeks.[12,26] In our previous study in which 0.03% mouthwash was used, we observed a complete remission in 19% and 33% of 21 patients, while a partial or major response was found in 48% and 50% of cases after 2 and 6 months respectively.[13]

Two prospective analyses reported a complete or partial response in 95% of 40 enrolled patients and 80% of 15 patients after both 2 months, while another report noted a significant clinical improvement in 75% of 20 patients who received tacrolimus 0.1% ointment over 3 months.[28–30] In addition, Hodgson *et al.* examined 50 patients in a prospective study with a follow-up of 2–39 months (median: 19.8 months). Complete resolution, partial response and no response were noted in 14%, in 80% and in 6% of cases respectively.[20]

However, the clinical and methodological heterogeneity across these various studies makes any comparison difficult.

Our observed initial subjective improvement rate under therapy of 98.2% is in line with the findings of two other studies, in which subjective improvement was noted in 100% and 89% of cases.[12,16] However, a substantial number of our patients continuously reported moderate symptoms. Therefore, subjective remission (no impairment) was only achieved in 15.9% after 3 months of therapy. Noteworthy, this rate improved over time with 48% after 6 months and 70.9% after 12 months.

An interesting observation is the discordance between the objective and subjective improvement. With a Cohen's kappa of 0.42 (95% CI 0.33–0.51), the two parameters only showed a moderate agreement. Consequently, the clinical image did not necessarily correlate to the level of pain. This variation in individual perception underlines the importance of considering both the subjective improvement as well as clinical remission as treatment objectives.

The cumulative recurrence rate of 75.1% after complete cessation of tacrolimus in 17 patients is similar to previous studies describing 50% up to 76.5%.[11,12,26,31–33]

Only a small group of five patients (8.7%) reported adverse effects over the whole observation period, except for one case with therapy limiting nausea, all being minor like burning sensation and dysgeusia. This is in contrast to previous studies which noted much higher rates of side-effects,[12,28,33] but used 0.1% tacrolimus ointment.

We identified a SCC in four patients (7.0%), while the estimated overall incidence of malignant transformation for OLP is 1.37%.[34] This comparatively high rate might indicate a direct causality between prolonged use of tacrolimus and development of SCC, as it has been claimed in previous case reports.[35,36] However, malignant transformation varies considerably among studies and the real risk related to OLP or its treatment remains

unknown.[34,35,37–39] Chronic inflammation as a cause of carcinogenesis has been demonstrated in various diseases, possibly explaining why patients with erosive forms of OLP more often show a malignant transformation.[34,37,39] Similarly, our cohort consisted of patients referred to a tertiary centre with an already more severe and chronic disease, including 87.7% with an erosive form of OLP, suggesting that they were overall more at risk for SCC.[34] Furthermore, one patient with 30 years of nicotine abuse was diagnosed only 1 month after initiation of tacrolimus, while another one already had a history of SCC.

Altogether, there is currently no sound evidence indicating that tacrolimus affects the inherent risk of OLP for malignant transformation, although this possibility cannot be excluded.[35,36,38–40] In this context, a recent meta-analysis did not find an association between the use of topical calcineurin inhibitors and an increased risk of keratinocyte carcinomas.[41] Another study even postulated a significantly lower risk for oral carcinogenesis under tacrolimus through cell cycle control *via* induction of G1/S phase arrest and therefore inhibition of epithelial cell proliferation and tumour formation.[42] Nonetheless, also based on the observed high rate of malignancies in our series, regular follow-up of patients with erosive OLP during treatment remains fundamental to recognize malignant transformation in an early stage.

The major limitation of this study is its retrospective design with no control group and accordingly no systematic follow-up. The used 0.03% tacrolimus rinse may limit direct comparison to other studies with different preparations. Furthermore, measurement of tacrolimus serum levels was not part of the study protocol. The substantial loss to follow-up is explained by the referral for further supervision by family doctors or dentists after clinical improvement. To better characterize the efficacy and the optimal long-term therapeutic scheme of topical tacrolimus in OLP management as well as to determine a cause-effect relationship of tacrolimus and malignant transformation, a large prospective RCT with a systematic follow-up remains necessary.

Conclusion

Topical tacrolimus can be a valuable option as a second-line treatment for OLP refractory to potent topical corticosteroids. Once OLP is satisfactorily controlled with twice daily tacrolimus mouthwash, the frequency can be reduced to a maintenance therapy aimed at preventing relapses. Both signs of clinical activity as well as subjective discomfort and pain should guide therapy. Complete discontinuation is possible in a minority of patients. Regular follow-up is mandatory to recognize malignant transformation in early stage.

IRB approval status

Reviewed and approved by the ethics committee of the Canton of Bern (KEK-2020-02577).

Patient privacy

The patients in this manuscript have given written informed consent to publication of their case details.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Severity and measures of clinical improvement at follow-up in the study population.

Table S2 Therapy regimen at baseline and follow-up.