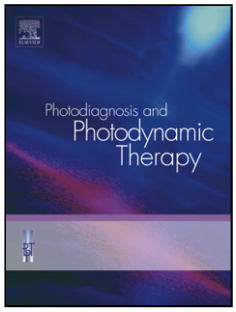

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Preliminary evaluation of the utility of optical coherence tomography in detecting structural changes during photobiomodulation treatment in patients with atrophic-erosive oral lichen planus.

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Short Title: Optical Coherence Tomography in OLP patients.

Highlights

- Oral Lichen Planus (OLP) is an inflammatory disorder requiring treatment if painful
- Clobetasol and photobiomodulation (PBM) are often provided as treatment
- Optical Coherence Tomography (OCT) provides a real-time, non-invasive investigation
- OCT was used to explore changes induced by PBM and clobetasol in 40 OLP patients
- OCT detected fluctuation of width of epithelium and lamina propria, in each group

Abstract

*Introduction***:** Oral lichen planus (OLP) is a common oral inflammatory condition. Against symptomatic atrophic-erosive OLP, topical steroids, or photobiomodulation (PBM) are deployed. Optical coherence tomography (OCT) provides a real-time, non-invasive, tissue investigation. ~~For the first time ever,~~ Aim of this study was to evaluate modifications of OCT pattern in patients with painful atrophic-erosive OLP, before and after treatment with PBM, comparing those results with patients treated with topical steroid.

Methods: Two groups of 20 OLP patients were evaluated. Group A underwent two daily application of 0.05% clobetasol propionate for 8 weeks; group B was treated with eight weekly PBM sessions using a 980/645 nm diode laser. OCT scans were performed before and after treatment, and six months after end of the proposed protocol. Changes of width of stratified epithelium (EP) and lamina propria (LP) were quantified.

Results: After 8-weeks, both groups experienced a significant increase of EP width ($p < 0.05$), and a significant decrease of LP width ($p < 0.05$), with Δ-EP in Group A significantly higher than Group B ($p = 0.0015$); conversely, Δ-LP was not significantly different ($p > 0.05$). After six months, significant increase of EP width remained only in group B ($p = 0.01$), with no significant decrease of LP mean width in both groups ($p > 0.05$).

Conclusions: Increase of EP and decrease of LP might be explained as consequence of clobetasol and PBM ability to promote epithelial healing, and to reduce interface inflammation. When investigated with OCT, clobetasol appears to provide more significant short-term structural changes, whereas PBM might guarantee long-term alterations.

Keywords: OCT, optical coherence tomography; OLP, Oral Lichen Planus; treatment; photobiomodulation; clobetasol propionate.

1. Introduction

Since its first report published in 1991, Optical Coherence Tomography (OCT) became a reliable diagnostic tool in various fields of medicine, where a partially coherent beam of near-infrared light waves interacting with tissues' components and a Michelson or Mach-Zehnder interferometer provides real-time images with excellent axial resolution [1,2].

OCT has become a reliable tool for diagnosis, management and prognostic evaluations in ophthalmology, in the identification of non-melanoma skin cancer in dermatology, with an increasing deployment increasingly in cardiology, gastroenterology, pulmonology, and oncology [3].

Since the first attempts in 1998 [4], OCT has been tested in dentistry. In restorative dentistry, OCT proved its reliability in early diagnosis of caries, allowing a safer diagnosis X-ray radiography, and providing in-depth evaluation of restoration integrity [5,6]. In periodontology, OCT showed accurate imaging of gum margins, periodontal pockets, and attachments, offering insights in the management of periodontitis [7]. In implantology, OCT showed effectiveness in determining the misfit of implant-abutment interface [8].

Concerning oral medicine, OCT has been mostly tested to describe the main ultrastructural characteristics of oral cancer [9,10], showing potential applications in vesicular-bullous disorders [11] in vascular lesions, and bone-related disease [12]. On the other hand, there is very limited evidence on the effectiveness of OCT in early detection or therapeutic management of oral premalignant disorders (OPMD). Among OPMDs, the most common entity experienced in the everyday clinical practice is represented by Oral Lichen Planus (OLP), a chronic

mucocutaneous inflammatory disease with a wide range of clinical manifestations, either as asymptomatic, white reticular/plaque lesions or as painful, red atrophic-erosive lesions [13,14].

As confirmed in a recent systematic review, [15] OLP is to be considered an OPMD, with an overall transformation rate into oral squamous cell carcinoma of 1.40% and erosive type as a potential risk factor. To date, various therapies have been proposed for the clinical management of atrophic-erosive OLP, mainly in the form of high-potency topical steroids. The first line of treatment ~~such as~~ consists of 0.025-0.05% clobetasol propionate, whereas topical calcineurin inhibitors, such as 0.1% tacrolimus and 1% pimecrolimus are administered as second-line treatment [16]. Among the reliable alternative to these formulations, usually delivered as ointments, photobiomodulation (PBM) protocols provided growing evidence of efficacy, with different laser types (ultraviolet, helium-neon and diode) deployed for multiple sessions [17,18]. However, no evidence of OCT ultrastructural changes of OLP oral mucosae has been provided, so far, particularly during the exposure to these protocols. Recently, we ~~provided~~ detailed some preliminary insights on the differential OCT pattern of healthy and OLP-affected buccal mucosa, using their histopathological counterparts as gold standard [19], as first step of a pilot study exploring reliability of OCT in oral medicine. As second step, the present work aims to evaluate the differential spectrum of OCT morphometric features within buccal mucosa of a group of patients affected by painful atrophic-erosive OLP, undergoing an 8-week protocol of PBM, and to compare these preliminary findings with those of a comparison group, undergoing a gold-standard treatment with 0.05% clobetasol propionate.

2. Material and Methods

2.1 Patients

Consecutive Caucasian patients were enrolled. The inclusion criteria were: a) histological diagnosis of OLP (e.g. hyperkeratosis of the superficial epithelial layers, vacuolar degeneration of the germinative layer of the epithelium and band-like sub-epithelial lymphocytic inflammatory

infiltrate) [20]; b) presence of painful, atrophic-erosive oral lesions; c) ability to complete the present protocol. The exclusion criteria were: a) presence of histological signs of dysplasia; b) use of drugs potentially inducing a lichenoid reaction; c) presence of amalgam fillings close to lesions; d) therapy for OLP in the 2 months timespan prior to the study; d) pregnant or breast-feeding women; e) proved or suspected hypersensitivity caused by the tested chemicals.

~~Two groups (Group A and B) of 20 patients each were forged, selected prospectively between those affected by erosive and painful OLP, referred to the Unit of Oral Medicine, CIR Dental School, University of Turin (Group A = from 1 to 20; 13 F; 7 M; mean age: 59.34 years; Group B = from 21 to 40; 12 F; 8 M; mean age: 63.56 years). Each patient was informed of our protocol and signed an informed consent, whenever keen to participate.~~

2.2 Therapy

Group A underwent eight weeks "gold-standard" treatment with two daily application of clobetasol dipropionate 0.05% in an aqueous gel of 4% hydroxyethyl cellulose (100 g) in equal parts (50:50) [20]. Group B was exposed to eight PBM sessions, once a week for eight weeks, delivered with a 980/645 nm Aluminium Gallium Arsenide (AlGaAs) diode laser ("Raffaello" Diode Laser, distributed by DMT S.r.l., Via Nobel 33, 20035, Lissone, Italy). Patients would receive PBM with 980 nm wavelength alone, as in a previous work, where such wavelength was tested to assess PBM efficacy against atrophic-erosive OLP unresponsive to topical steroids [21]. The device was used with the following parameters: output power = 400 mW, power density = 0,8 W/cm^2, fluence = 8 J/cm^2, Energy = 4 J. The collimated probe, emitting a Gaussian beam, had a spot size of 0.5 cm^2, and was kept perpendicularly at 2 mm from the area of irradiation. A "spot" technique would be carried out in each site, with a slight overlapping pursued to compensate for the Gaussian beam emission both on the mucosal lesions and the perilesional tissues, up to 0.5 cm for 10 seconds. Fluence of 8 J/cm^2 was considered the most

appropriate for the purposes of the present study, being found as more effective ~~for~~ for healing process, due to an higher propensity for deposition of collagen, according to animal models [22]. Despite such overlapping approach might have caused an increase of fluence up to 20%, PBM could be still administered within the therapeutic window of 0.01-10 J/cm^2, as indicated by Arndt-Schulz law, with fluence ranging from 8 to 9.6 J/cm^2 on each site.

2.3 OCT system

Two types of scans were acquired: "enface" scans – duration: 12 seconds; frames: 120; depth: 6 mm – and "dynamic" scans – duration: 30 seconds, number of frames: 120, depth: 6 mm. The specifics and the parameters of the machine (SSOCT, VivoSight® Michelson Diagnostics Ltd, version 2.0, Orpington, Kent, UK) deployed for the present study have already been specified [19].

2.4 OCT measurements

OCT scans were performed before treatment protocol, and repeated at the end of the 8-weeks treatment protocols in both groups. Clinical photographs of the lesions were ~~acquired~~ taken before and after treatment. The changes of width within the stratified epithelium (EP) and the lamina propria (LP) were standardized as follows:

- The 60th frame of enface and ~~or~~ dynamic scans were taken as "gold standard" for the analysis, being at the exact center of the 120 scans provided by the OCT device deployed in the present work, coinciding with the exact centre of the lesion, and being as much refined as possible from artefacts either caused by patients' sudden movements or by clinician's excessive pressure, occurring at the beginning or at the end of the scanning process, as it can be observed in the first or last frames of the scan.
- EP width of the 60th frame was regularly measured through the dynamic scan as follows: the light-grayish, hyporeflective, homogeneous area intertwined between the

plastic wrapping, and the level at which the peak of the red spikes occurred most frequently, thus indicating the transition from the epithelium to the underlying vascularized tissue of LP, as the thinnest suprapapillary plate (Fig.1)

- LP width of the 60th frame was regularly measured through the dynamic scan as follows: the hypo-reflective red area intertwined between the most recurring peak of the red spikes, and the most recurring position of the base of the red spikes, thus indicating the transition between LP and the homogenous, unreadable dark area (Fig.2).

2.5 Statistical analysis

Paired t-student test was conducted to evaluate the variations of EP and LP width within Group A and Group B, both at the end of treatment, and six months after the end of treatment. On the other hand, unpaired t-student test was performed to evaluate differences in fluctuations of EP (Δ-EP) and of LP (Δ-LP) between Group A and B. Statistical analysis was performed using SAS ver 9.3, and 2-tails p-value less than 0.01 was considered statistically significant.

3. Results

Two groups (Group A and B) of 20 patients each were forged, selected prospectively between those affected by erosive and painful OLP, referred to the Unit of Oral Medicine, CIR Dental School, University of Turin (Group A = from 1 to 20; 13 F; 7 M; mean age: 59.34 years; Group B = from 21 to 40; 12 F; 8 M; mean age: 63.56 years). Each patient was informed of our protocol and signed an informed consent, whenever keen to participate.

3.1 Group A: clobetasol propionate

Group A revealed a significant variation of both EP and LP between the beginning and end of the 8-weeks protocol with clobetasol propionate÷. Specifically, EP experienced an overall

increase after treatment, from a mean width of 0.14 (±0.02) mm to 0.19 (±0.03) mm. Paired t test revealed a two-tailed P value <0.001 (95% CI: −0.0651; −0.0379), suggesting a statistically significant increase of EP width. (Table 1). On the other hand, LP experienced an overall decrease after clobetasol treatment, shifting from a mean width of 0.68 (± 0.04) mm to 0.64 (± 0.04) mm. Paired t test revealed a two-tailed P value <0.001 (95% CI: 0.0183;0.0537), suggesting a statistically significant decrease of LP width. (Table 1). Figure 3 shows the variation of EP and LP in patient 1, before and after treatment. Figure 4 shows clinical appearance of patient 1 before and after treatment with clobetasol. Clinically, only 12 of 20 (60%) were able to undergo no treatment for six months, with the remaining eight (40%) patients forced to recur to clobetasol treatment (four patients: 1 month later, three patients: between 2 and 4 months; one patient: 5 months later): thus, the measurements were acquired and registered only in 12 cases. Bearing this 40% dropout rate in mind, six months after end of treatment, the aforementioned variations were not maintained, with EP and LP width showing an almost overlapping pattern to pre-therapy measurements. Specifically, EP values after six-months displayed a mean value of 0.145 (± 0.02) mm, very close to mean width of 0.143 (±0.03) mm registered by these 12 patients before therapy. Paired t test revealed a two-tailed P value = 0.63 (95% CI: −0.0137; 0.0087), suggesting no statistically significant differences for EP width (Table 2). Figure 5 shows the variation of EP and LP width between the beginning and the end of the six months protocol, as well as the clinical appearance at end of protocol. Similarly, LP measurements after six months displayed an overlapping pattern to those registered in these 12 patients before treatment, with a mean value of 0.6608 (± 0.04) mm, being very close to a mean pre-treatment width of 0.674 (± 0.04) mm. Paired t test revealed a two-tailed P value = 0.5 (95% CI: (−0.0554; 0.0287), suggesting no statistically significant differences. (Table 2).

3.2 Group B: PBM

As in Group A, Group B measurement experienced a significant variation of both EP and LP between the beginning and the end of the 8-weeks PBM protocol: Specifically, EP experienced an overall increase after the treatment, from a mean width of 0.16 (±0.02) mm to 0.18 (± 0.02) mm.

Paired t test revealed a two-tailed P value < 0.001 (95% CI:−0.331; 0.012), suggesting a statistically significant increase of EP width. (Table 1). On the other hand, LP experienced a decrease after PBM treatment, diminishing from a mean width of 0.69 (± 0.04) mm to 0.66 (± 0.04) mm. Paired t test revealed a two-tailed P value = 0.007 (95% CI: 0.0104; 0.0566), suggesting a statistically significant decrease for LP width. (Table 1). Figure 6 shows the variation of EP and LP in patient 2 before and after treatment. Figure 7 shows clinical appearance of patient 2 before and after PBM treatment. Clinically, only 13 of 20 (65%) were able to undergo no treatment for six months, with the remaining 7 patients forced to recur to treatment during the last phase of the six-months protocol, either as a second cycle of PBM (4 patients), or as clobetasol treatment (1 patients), or as systemic treatment in the form of prednisone tablets (2 patients). Thus, the measurements were acquired and registered only in 13 cases. Bearing this 35% dropout-rate in mind, six months after the end of PBM treatment, EP showed a persisting and significant increase, when compared to pre-therapy values. Specifically, EP values after six-months displayed a mean value of 0.18 (± 0.03) mm, against a mean width of 0.16 (± 0.03) mm registered before therapy. Paired t test revealed a two-tailed P value = 0.01 (95% CI: −0.0119; 0.0165), suggesting a statistically significant difference of EP width. (~~Table 3~~ Table 2). Conversely, LP measurements after six months displayed an overlapping pattern to that registered before treatment, with a mean value of 0.695 (± 0.04) mm, being very close to a mean pre-treatment width of 0.686 (±0.04) mm. Paired t test revealed a two-tailed P value = 0.35 (95% CI: −0.0274; – 0.0105), suggesting no statistically significant differences. (~~Table 3~~ Table 2). Figure 8 shows the variation of EP and LP width between the

beginning and the end of the six months protocol, as well as the clinical appearance at end of protocol.

3.3 Group A vs Group B at the end of 8-weeks treatment

A comparison was conducted between Group A and Group B, with the aim to assess if there were any significant differences concerning the fluctuations of EP and LP width after the 8-weeks protocols. Therefore, the fluctuations of EP (Δ-EP) and LP (Δ-LP) width before and after treatment were calculated for both Group A, and Group B. Secondly, the Δ-EP and Δ-LP obtained were compared through an unpaired t-Test. Group A experienced a mean Δ-EP of 0.05 (±0.03) mm, whereas Group B experienced a mean Δ-EP of 0.02 (± 0.02) mm. Unpaired t-test revealed a two-tailed P value P = 0.0015 (95% CI: 0.0119; 0.0461), suggesting a statistically significant difference between the two groups (Table 3). Group A experienced a mean Δ-LP of –0.028 (± 0.04) mm, whereas Group B experienced a mean Δ-LP of –0.030 (± 0.05) mm. Unpaired t-test revealed a two-tailed P value P = 0.87 (95% CI: –0.0282; 0.0332), suggesting no statistically significant difference between the two groups (~~Table 4~~ Table 3).

4. Discussion

The present study carried out an evaluation of morphometric changes with OCT of the oral tissues of patients with painful, atrophic-erosive OLP undergoing PBM (Group A), compared to 0.05% clobetasol propionate (Group B). According to our analysis, both PBM and 0.05% clobetasol propionate were able to provide a significant modification of the oral mucosa and of the epithelium-connective interface, detectable as changes of EP and LP width.

Regarding EP, an increase of the overall width emerged, suggesting the efficacy of both treatments in promoting the resolution of the epithelial atrophy, through a progressive restore of the epithelium turnover. On the contrary, a significant reduction of the LP area was found, which instead might be indicative of the anti-inflammatory effect provided by both treatments,

experienced as a temporary reduction of the band-like inflammatory cell infiltrate below the epithelium basal cells.

When comparing the results of these fluctuations between the two groups, contrasting results were obtained: Group A exposed to clobetasol propionate seemed to experience a significantly higher increase of EP width, when compared to Group B undergoing PBM treatment, at end of treatment. On the other hand, in Group B there was a significant persistence of higher EP values, when compared to pre-treatment parameters, up to six months after treatment end. Finally, such differential fluctuation were not detected as LP width, which displayed an overlapping behaviour in the two groups, throughout the eight months of the study.

The main strength of the present work relies in the novelty of evidence provided. Despite some recent evidence emerged on the anti-inflammatory in vitro effects of PBM on human gingival fibroblasts (HGF), both as stimulation of vascular endothelial growth factor (VEGF) and decrease of tumor necrosis factor alpha (TNF-α) [23], this is the first attempt to investigate OCT structural changes elicited by PBM in vivo, rather than in vitro, providing a comprehensive change of pattern. No evidence is so far available in literature concerning the differential OCT profile of oral mucosa before and after surgical/medical treatment among patients with OLP, or other OPMDs.

Regarding clinical investigations, apart from an isolated study focused on the main ocular findings of Lichen Planus through a spectral domain OCT [24], there seem to be scarce data on the reliability of OCT for in-vivo diagnosis of OLP, with sensitivity and specificity so far tested instead for oral dysplasia or oral carcinoma, mostly from ex vivo analysis [25-27]. Nevertheless, none of these works offered evidence of ultrastructural alterations before and after a specific treatment protocol for either OLP, or other OPMDs.

Furthermore, there is scarce clinical evidence in literature regarding the differential effectiveness of topical corticosteroids compared to PBM, which is yet to be clarified, as our OCT findings suggest. Concerning this aspect, a recent systematic review by Akram and co-

workers [28], conducted to assess the efficacy of PBM against corticosteroids in the treatment of OLP, provided weak and debatable evidence, with only one trial, with moderate risk of bias, deploying 0.05% clobetasol as topical steroid treatment and compared with PBM. In this paper, PBM was able to provide significant improvement than topical corticosteroid beyond end of treatment, at the subsequent follow-up visits [29].

Despite these clinical evidences appear somehow converging with the long-term OCT alterations detected in our PBM group, such convergence must be interpreted cautiously, since it arises from a combination of outcomes ,obtained through divergent approaches - one purely clinical, the other mediated by OCT - acquired, in both cases, from small samples of patients, with a preliminary, subjective method of quantification of EP and LP width.

Apart from the limited number of patients enrolled, other main limitations of the present study can be enunciated firstly as OCT-related, such as its expensiveness, the potential inappropriateness of the flat oral probe deployed for mucosal districts other than buccal mucosa, such as tongue, gingiva, and palate, as more extensively discussed in our previous study [19]. Secondly, some user-related issues should be pointed out, such as the need for a proper learning curve for the clinician, whose inexperience might generate artefacts, particularly if an excessive pressure or unsteadiness of the probe is pursued during the 30 seconds required to complete the scan.

5. Conclusion

OCT played a promising role in revealing the immediate efficacy of 0.05% clobetasol and PBM as treatment options for patients with atrophic-erosive OLP, by displaying a distinctive pattern of epithelium and connective tissue after the exposure to both of these treatments, with some preliminary evidence of long-term repercussions on epithelium by PBM, that need further investigation. Future studies should focus on larger samples of patient, and provide concurrent clinical and patient-related outcomes, to understand the reliability of these OCT preliminary

findings. Ideally, OCT should be tested to investigate other clinical entities, such as other OPMDs, or autoimmune bullous-erosive disorders requiring constant follow-up or/and therapy, to fully understand if OCT should be introduced as a regular tool to improve the quality of healthcare in oral medicine.

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Table 1. Mean, Standard deviation, Standard error of mean, and p-value of EP and LP width variations in Group A (clobetasol) and Group B (Photobiomodulation, PBM) - before and after 8-weeks protocols.

Statistical parameters	**EP width before clobetasol (mm)**	**EP width after clobetasol (mm)**	**EP width before PBM (mm)**	**EP width after PBM (mm)**	**LP width before clobetasol (mm)**	**LP width after clobetasol (mm)**	**LP width before PBM (mm)**	**LP width after PBM (mm)**
Sample size	20	20	20	20	20	20	20	20
Mean	0.1445	0.1960	0.1595	0.1820	0.6785	0.6425	0.6910	0.6575
SD (standard deviation)	0.0239	0.0319	0.0274	0.0250	0.0436	0.0386	0.0433	0.0442
SEM (standard error of mean)	0.0054	0.0071	0.0061	0.0056	0.0097	0.0086	0.0097	0.0099
p-value (95% CI)	<0.001 (−0.0651; −0.0379)		<0.001 (−0.331; 0.012)		<0.001 (0.0183; 0.0537)		0.007 (0.0104; 0.0566)	

Table 2. Mean, Standard deviation, Standard error of mean, and p-value of EP and LP width variations in Group A before clobetasol treatment, and six months after end of treatment.

Statistical parameters	**EP width before clobetasol (mm)**	**EP width six months after end of clobetasol (mm)**	**LP width before clobetasol (mm)**	**LP width six months after clobetasol (mm)**
Sample size	12	12	12	12
Mean	0.1433	0.1458	0.6608	0.6742
SD	0.0257	0.0188	0.0401	0.0421
SEM	0.0074	0.0054	0.0158	0.0122
p-value (95% CI)	0.63 (−0.0137; 0.0087)		0.5 (−0.0554; 0.0287)	

Table 3. Mean, Standard deviation, Standard error of mean, and p-value of EP and LP width variations in Group B before therapy and six months after the end of PBM treatment.

Statistical parameters	**EP width before PBM treatment (mm)**	**EP width six months after PBM treatment (mm)**	**LP width before PBM treatment (mm)**	**LP width six months after PBM treatment (mm)**
Sample size	13	13	13	13
Mean	0.1600	0.1808	0.6869	0.6954
SD	0.0303	0.263	0.0433	0.0376
SEM	0.0084	0.0073	0.0120	0.0104
p-value (95% CI)	0.01 (−0.0119; 0.0165)		0.35 (−0.0274; 0.0105)	

Table 1. Statistical parameters before and after 8-week clobetasol (Group A) and photobiomodulation (PBM, Group B) treatment.

	Stratified Epithelium				**Lamina Propria**			
Statistical parameters	**Before Clobetasol**	**After Clobetasol**	**Before PBM**	**After PBM**	**Before Clobetasol**	**After Clobetasol**	**Before PBM**	**After PBM**
Sample size	20	20	20	20	20	20	20	20
Mean	0.1445	0.1960	0.1595	0.1820	0.6785	0.6425	0.6910	0.6575
SD	0.0239	0.0319	0.0274	0.0250	0.0436	0.0386	0.0433	0.0442
SEM	0.0054	0.0071	0.0061	0.0056	0.0097	0.0086	0.0097	0.0099
p-value (95% CI)	<0.001 (−0.0651; −0.0379)		<0.001 (−0.331; 0.012)		<0.001 (0.0183; 0.0537)		0.007 (0.0104; 0.0566)	

SD *(standard deviation),* ***SEM*** *(standard error of mean),* ***EP*** *(epithelium) ,****LP*** *(lamina propria),* ***PBM*** *(photobiomodulation).*

Table 2. Statistical parameters before and six months after clobetasol (Group A) and photobiomulation (PBM Group B) treatment.

	Stratified Epithelium				**Lamina Propria**			
Statistical parameters	**Before Clobetasol**	**After Clobetasol**	**Before PBM**	**After PBM**	**Before Clobetasol**	**After Clobetasol**	**Before PBM**	**After PBM**
Sample size	12	12	13	13	12	12	13	13
Mean	0.1433	0.1458	0.1600	0.1808	0.6608	0.6742	0.6869	0.6954
SD	0.0257	0.0188	0.0303	0.263	0.0401	0.0421	0.0433	0.0376
SEM	0.0074	0.0054	0.0084	0.0073	0.0158	0.0122	0.0120	0.0104
p-value (95% CI)	0.63 (−0.0137; 0.0087)		0.01 (−0.0119; 0.0165)		0.5 (−0.0554; 0.0287)		0.35 (−0.0274; 0.0105)	

SD *(standard deviation),* ***SEM*** *(standard error of mean),* ***EP*** *(epithelium)* ,***LP*** *(lamina propria),* ***PBM*** *(photobiomodulation).*

Table 3 4. ~~Mean, Standard deviation, Standard error of mean, and p-value of Δ-EP and Δ-LP in Group A and Group B.~~ Statistical parameters of epithelial (ΔEP) and lamina propria (ΔLP) fluctuations before and after 8-week clobetasol (Group A) and photobiomodulation (PBM, Group B) therapy.

Statistical parameters	**Δ-EP of Group A (clobetasol) (mm)**	**Δ-EP of Group B (PBM) (mm)**	**Δ-LP of Group A (clobetasol) (mm)**	**Δ-LP of Group B (PBM) (mm)**
Sample size	20	20	20	20
Mean	0.0525	0.0235	–0.0280	–0.0305
SD ~~(standard deviation)~~	0.0297	0.0235	0.0443	0.0513
SEM ~~(standard error of mean)~~	0.0066	0.0052	0.0099	0.0115
p-value (95% CI)	0.0015 (0.0119; 0.0461)		0.87 (–0.0282; 0.0332)	

SD *(standard deviation);* ***SEM*** *(standard error of mean);* ***EP*** *(epithelium);* ***,LP*** *(lamina propria);* ***PBM****: (photobiomodulation).*

Fig.1. OCT (dynamic scan): standardized method of EP measurement.

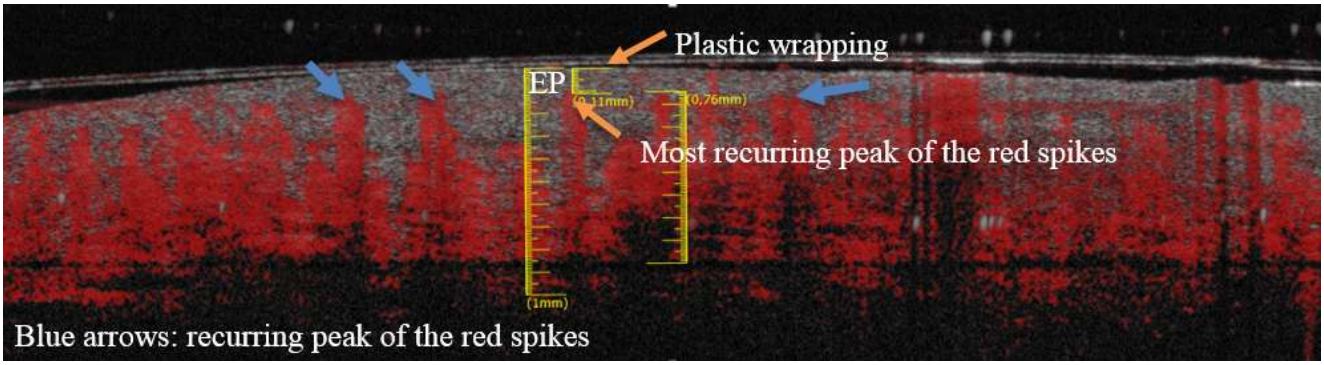


Fig.2. OCT (dynamic scan): standardized method of LP measurement.

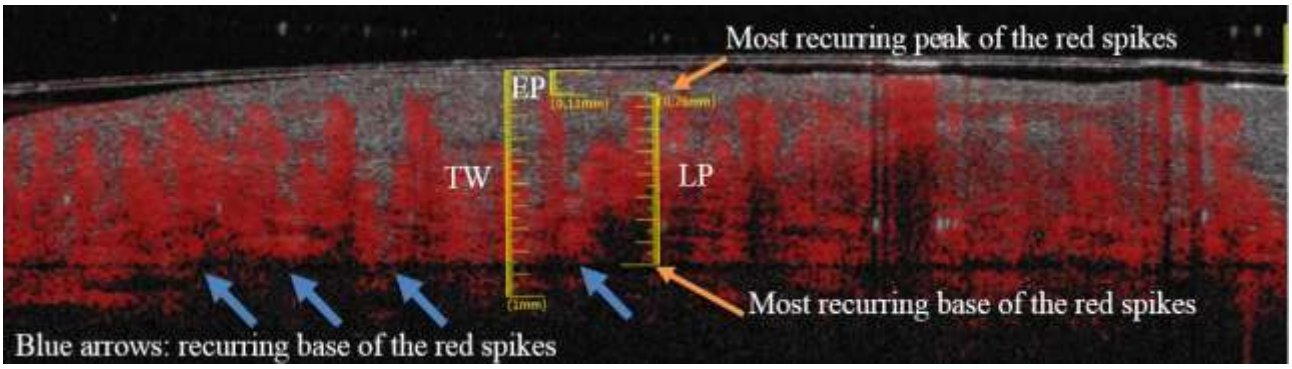
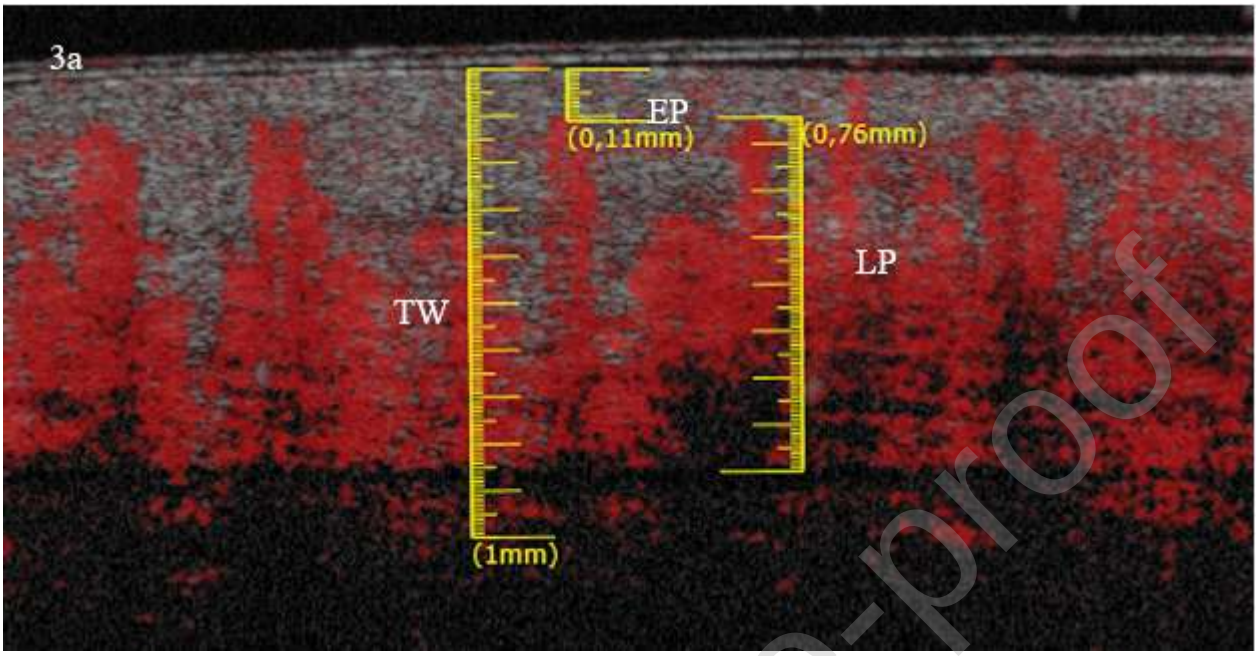


Fig.3. OCT (dynamic scan): Patient 1 of Group A (clobetasol): **3a**: EP and LP width before treatment; **3b**: EP and LP width after treatment. Notice the increase of EP (from 0.11 to 0.19 mm), and the corresponding decrease of LP (from 0.61 to 0.76 mm)



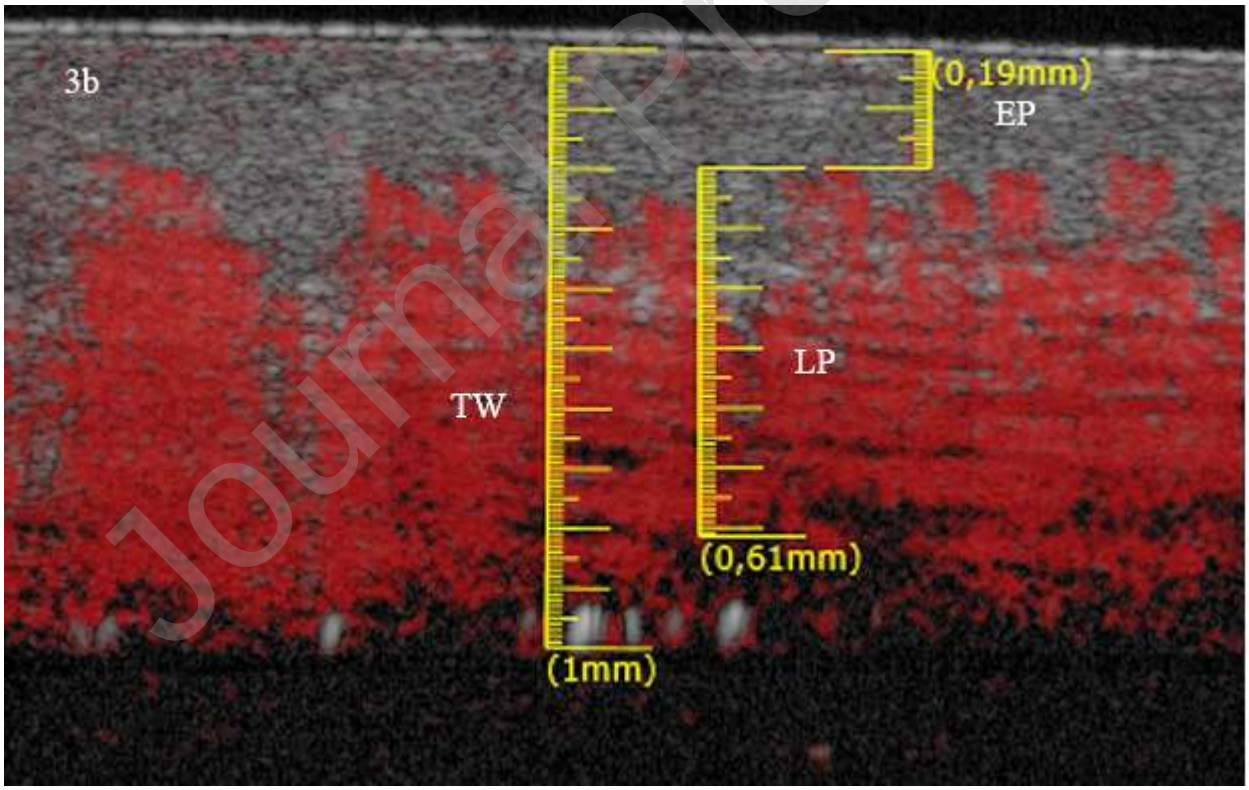


Fig. 4. Clinical appearance of patient 1 before (**4a**) and after (**4b**) clobetasol treatment

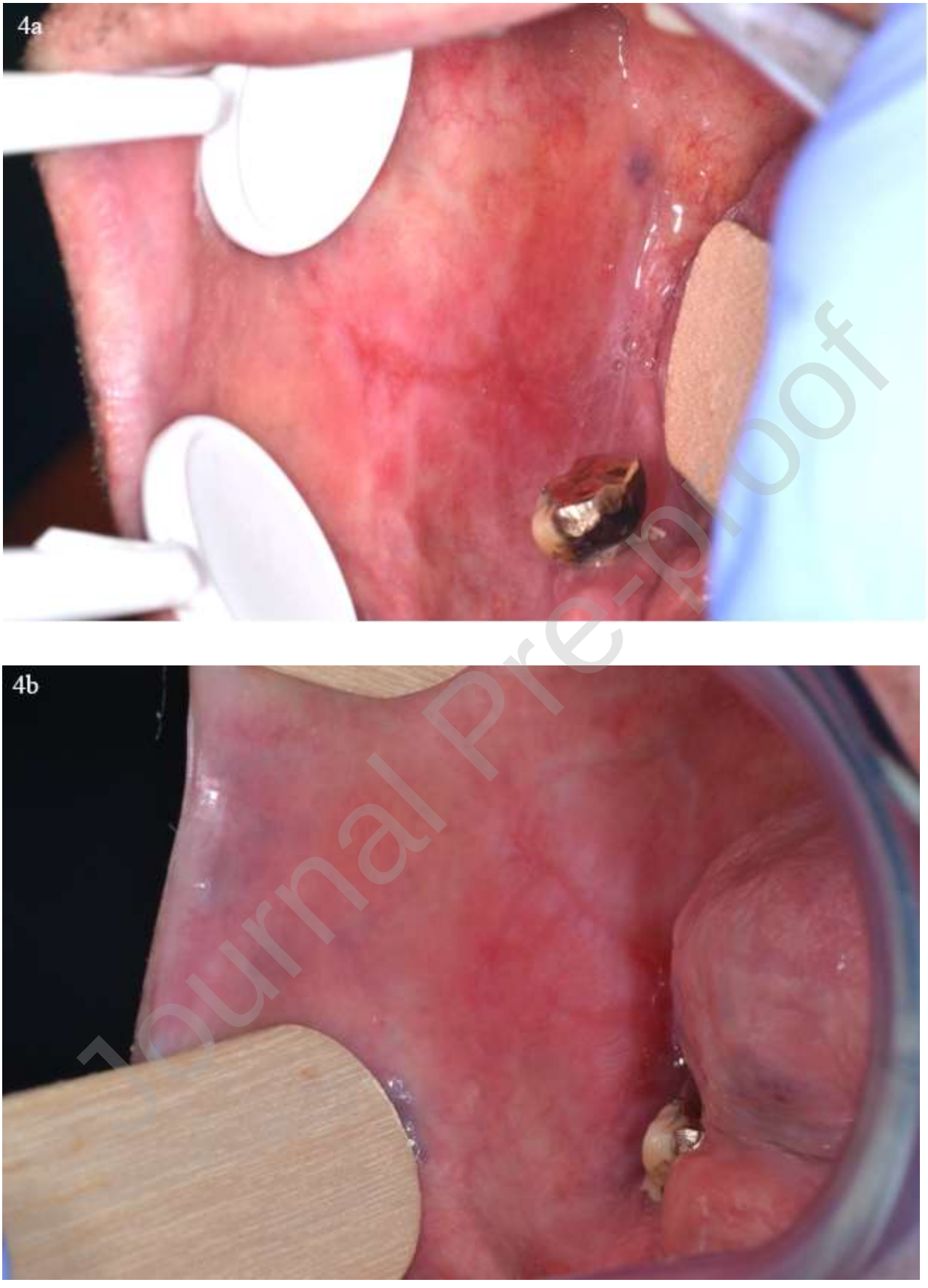
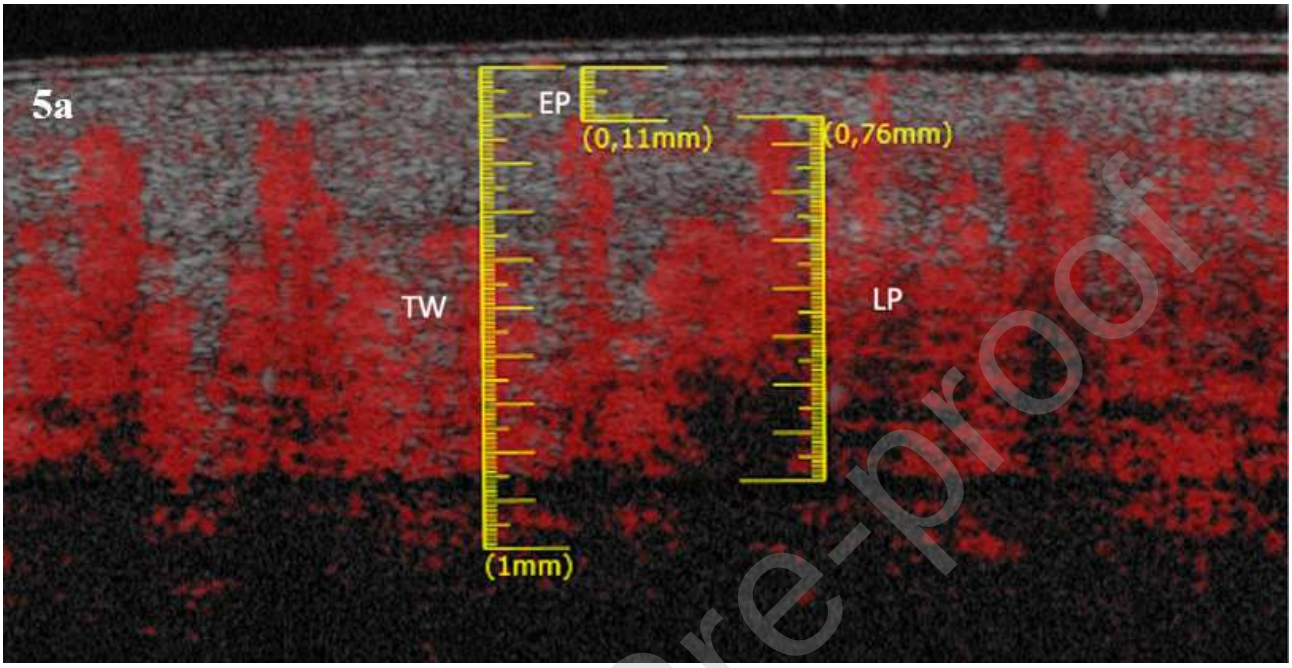
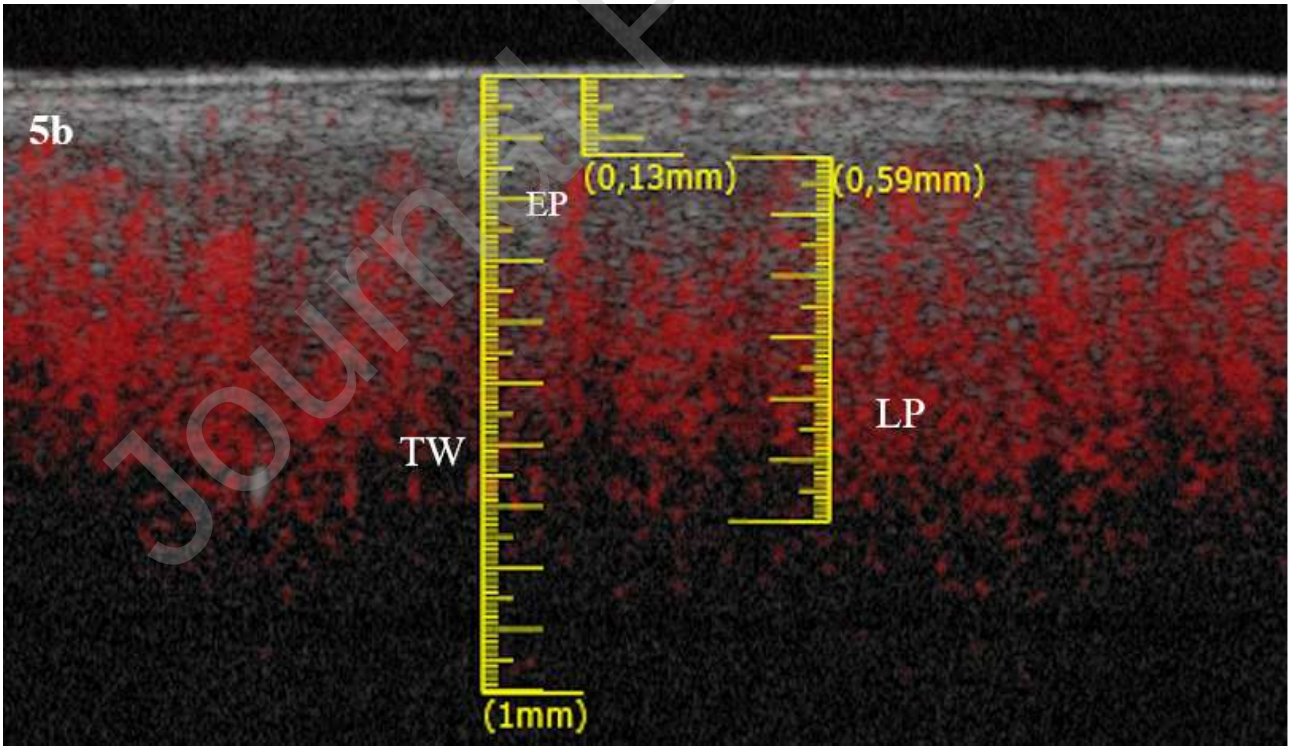


Fig.5: OCT (dynamic scan): Patient 1 of Group A (clobetasol): **5a**: EP and LP width before treatment; **5b**: EP and LP six months after end of treatment. Notice the increase of EP (from 0.11 to 0.13 mm) and the corresponding decrease of LP (from 0.76 to 0.59 mm), corresponding to a partial clinical improvement (**5c**) when compared to figure 4a.





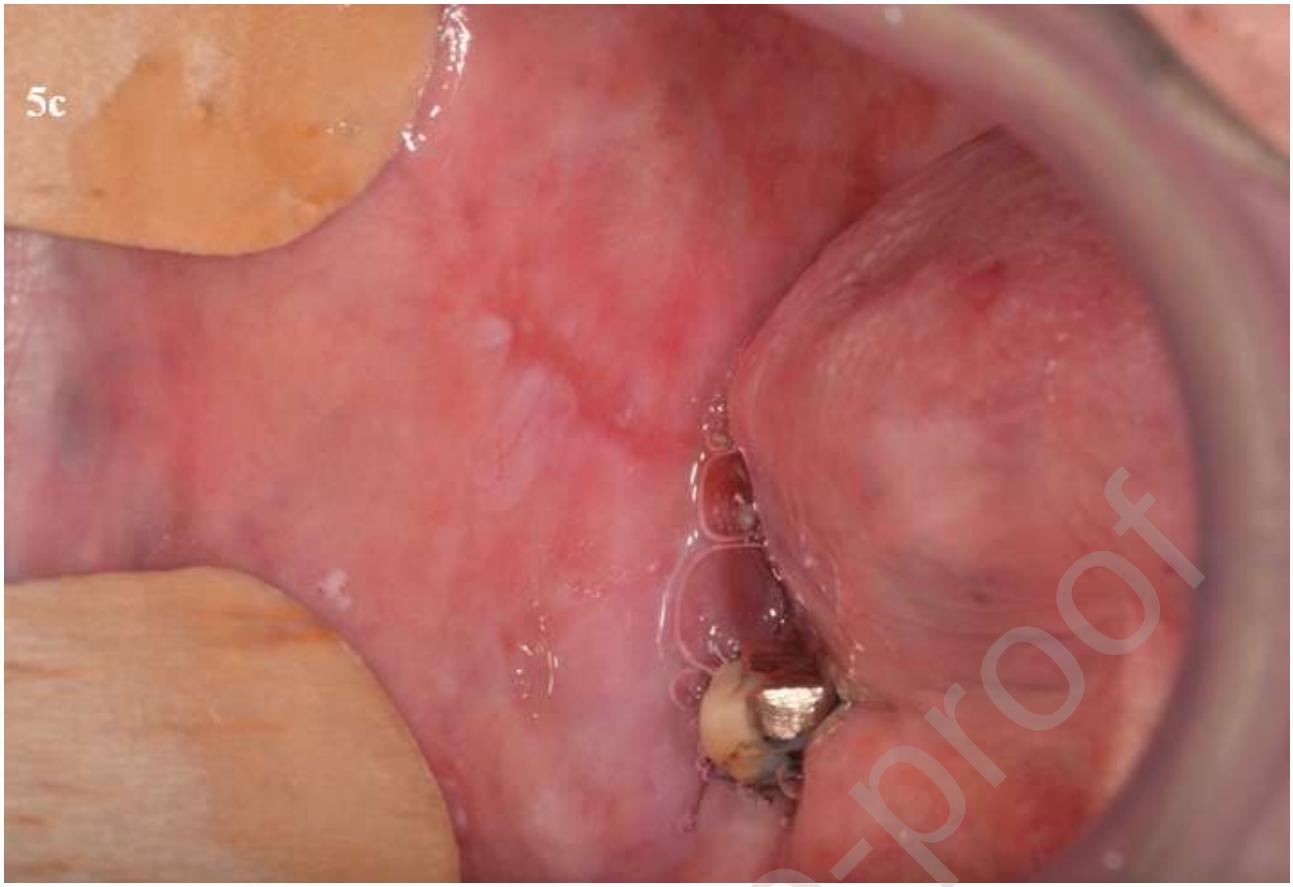
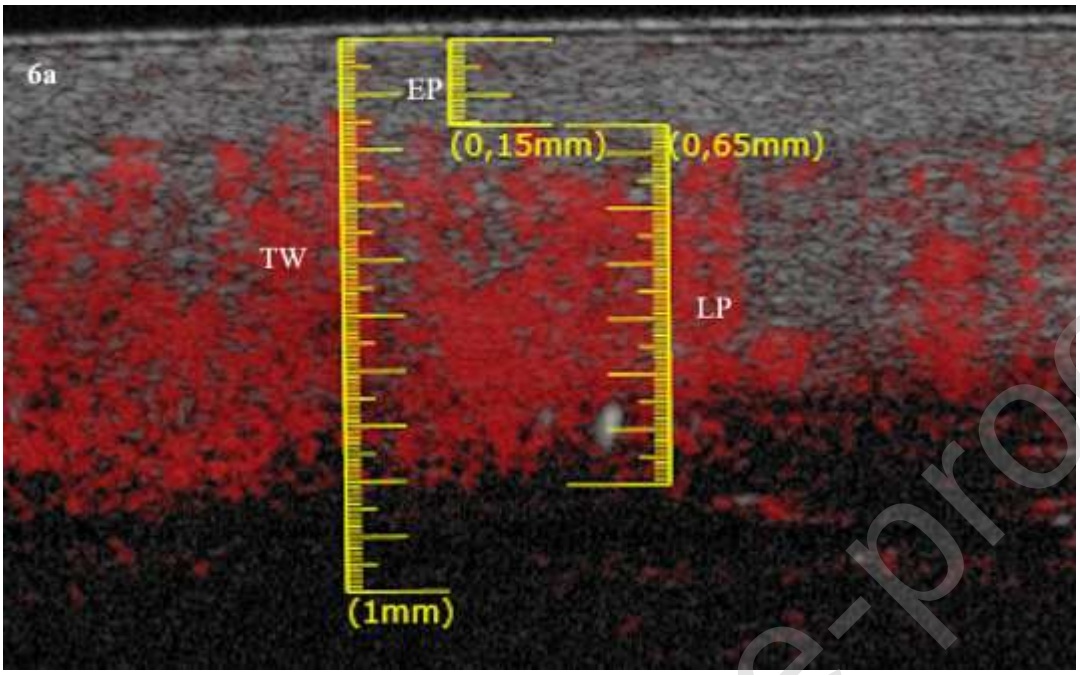


Fig. 6. OCT (dynamic scan): Patient 2 of Group B (PBM). **6a**: EP and LP width before treatment; **6b**: EP and LP width after treatment. Notice the decrease of EP (from 0.15 to 0.13 mm), and the corresponding increase of LP (from 0.65 to 0.72 mm).



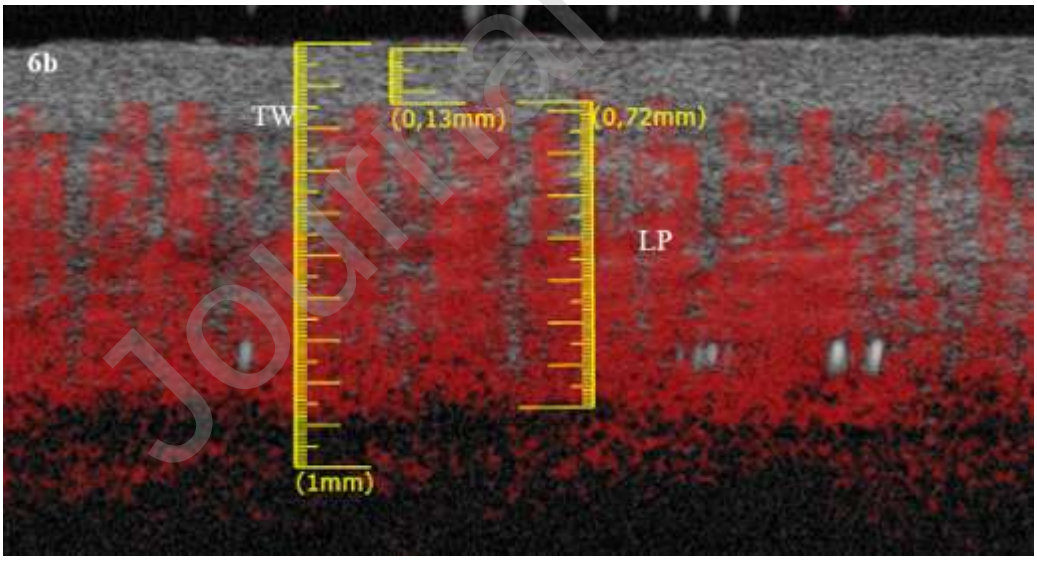
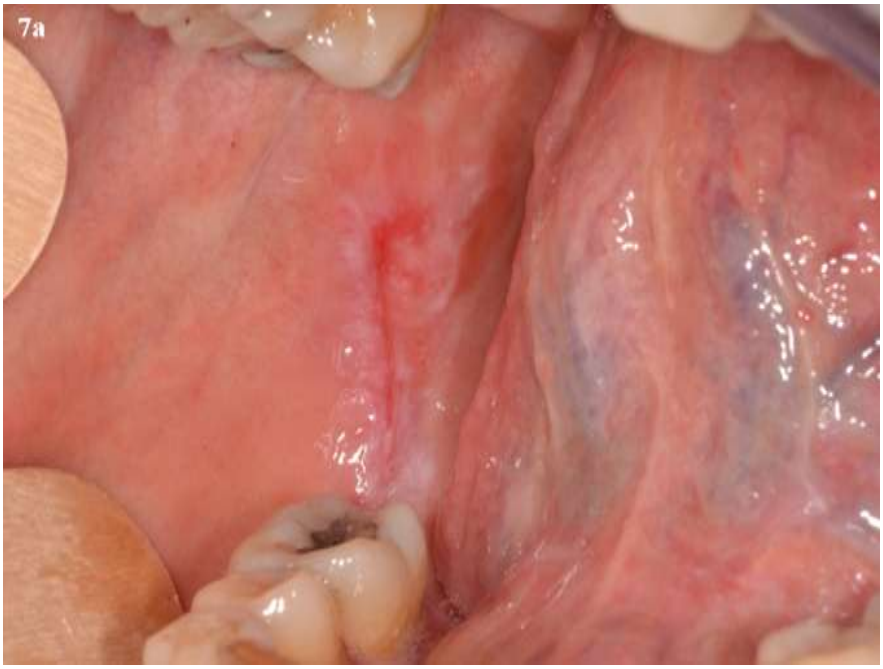


Fig. 7: clinical appearance of patient 2 before (7a) and after (7b) PBM treatment



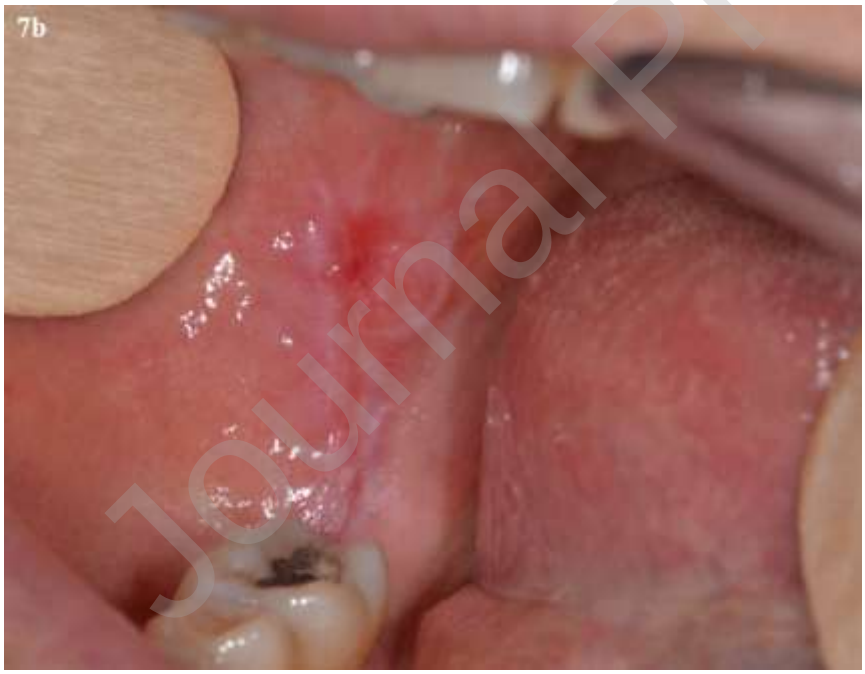


Fig.8. OCT (dynamic scan): Patient 2 of Group B (PBM): **8a**: EP and LP width before treatment; **8b**: EP and LP six months after end of treatment. Notice the further decrease of EP (from 0.15 to 0.1 mm), and the corresponding increase of LP (from 0.65 to 0.72 mm), corresponding to a partial clinical worsening (**8c**) when compared to figure 7a.