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Oral administration of a curcumin-phospholipid formulation (Meriva®) for treatment of chronic diabetic macular edema: a pilot study

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Abstract. – OBJECTIVE: The purpose of this open-label study was to investigate the effect of a curcumin-phospholipid lecithin formulation (Meriva®) on visual acuity and optical coherence tomography (OCT) retinal thickness in patients with chronic diabetic macular edema.

PATIENTS AND METHODS: Curcumin-phospholipid lecithin formulation (Meriva®, Indena S.p.A, Milan, Italy) was administered as tablets (Norflo®, Eye Pharma, Genoa, Italy) twice a day. Visual acuity and macular edema as measured by OCT before and after curcumin-phospholipid formulation treatment were assessed.

RESULTS: The study included 12 eyes from 11 patients who completed at least a 3-month follow-up period. After 3 months of therapy, no eyes showed reduction in visual acuity, 16% showed stabilization, and 84% showed improvement. The improvement was statistically significant (p = 0.0072). After 3 months of therapy, 92% of eyes showed reduction of macula edema, 8% showed stabilization, and 0% showed an increase (p = 0.009).

CONCLUSIONS: Our results, albeit preliminary, suggest that a curcumin-phospholipid formulation (Meriva®), administered as Norflo® tablets, may be feasible in the improvement of visual acuity and reduction of macular edema in patients with diabetic retinopathy.

Key Words:
Curcumin, Spectral Domain OCT, Retinal thickness, Visual acuity, Diabetic macular edema, Diabetic retinopathy, Meriva®.

Introduction

Diabetic macular edema (DME) is one of the most important complications in diabetic retinopathy (DR) and one of the leading causes of low vision in the population[1]. Many factors contribute to the pathogenesis of DME; however, one common feature is the increased levels of vascular endothelial growth factor (VEGF), which is responsible for the disruption of the inner blood-retinal barrier (BRB)[2]. BRB breakdown leads to the accumulation of retinal fluid with macular dysfunction. Moreover, hypoxia, ischemia, Muller glial cell and pericyte dysfunction and inflammatory mediators contribute to the pathogenesis of BRB damage and DME[3,4].

Curcumin is a bis-α,β-unsaturated diketone, which together with demethoxycurcumin and bisdemethoxycurcumin, constitutes the group of curcuminoids of the rhizome extract of *Curcuma longa*[5,6]. Curcumin has antioxidant and anti-inflammatory activity, with immediate relevance to many clinical conditions[7-12]. Moreover, curcumin has shown efficacy in animal models of acute and chronic inflammation of relevance to eye disease[4,13].

Taken together, these activities represent the rationale for studying the effect of curcumin in patients with DME. However, it is well-know that curcumin has poor systemic availability, and this issue greatly limits the use of curcumin in clinical practice. Over the last decade our group has developed a food-grade formulation of curcumin, in form of phytosome (Meriva®, Indena SpA, Milan, Italy; the use of the registered name in this paper is for clarity purposes only and does not imply endorsement)[14-16], with markedly improved adsorption after oral administration.

In this pilot study, we investigated the effect of Meriva® on visual acuity and optical coherence tomography (OCT) retinal thickness in patients with chronic DME.

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Patients and Methods

Patients

Inclusion criteria were clinically significant macular edema (CSME) in fundus examination, optical coherence tomography (OCT) and/or angiographic (Spectralis, Heidelberg Engineering, Heidelberg, Germany). All patients reported moderate to severe non-proliferative diabetic retinopathy (NDR) in fundus examination and had a fasting blood glucose test and *glycated hemoglobin* test (HbA1c) under control in the six months prior to enrolment. Diabetic eyes with opaque media preventing OCT imaging, history of intraocular surgery, intravitreal corticosteroids and/or anti VEGF therapy, macular or retinal photocoagulation within the previous 6 months, and those with choroidal neovascularization, were excluded.

Study Setting and Design

This study was a retrospective case series, conducted in patients with type 2 diabetes enrolled in an Italian tertiary Center from January to December 2016. All patients signed an informed and educated consent to the use of their data for research purposes, according to the standard practice of our Center. Patients were followed according to standard clinical practice, using standard diagnostic and intervention procedures, without any foreseeable risk for the evaluated subjects, and again only a notification to the Ethical Committee was required, in line with the practice of our Center.

Treatment

All patients received Meriva® 500 mg twice daily, representing a daily intake of 200 mg highly bioavailable curcuminoids (Meriva® being composed of one part curcuminoids, two parts lecithin from nongenetically modified soy, and two parts of microcrystalline cellulose). Meriva® was administered as a commercially available tablet formulation (Norflo®, Eye Pharma, Genoa, Italy).

Assessments

Spectral Domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was used for imaging with 3D macular scan protocol. An expert examiner (FM) performed all OCT examinations. OCT scans were segmented automatically by the segmentation algorithms incorporated in the Spectralis OCT software, which demarcates the internal limiting membrane (ILM) and the Bruch membrane (BM). A macular volume map was, therefore, generated. For the follow-up, the automatically-registered follow-up acquisition module was used in order to re-analyze the same macular area of the baseline.

Ophthalmological examination also included slit lamp examination. Early Treatment Diabetic Retinopathy Study best-corrected visual acuity measurement (Precision Vision, La Salle, IL, USA) for distance, Jaeger Test Type best visual acuity for near, intraocular pressure measurement and fundus examination using a Volk +90 D lens (VOLK Optical Inc., Mentor, OH, USA). Visual acuity for distance in LogMAR and for near in Jaeger were performed and macular volume was assessed. Clinical evaluations were performed at baseline and after 90 days of Meriva® treatment before and after treatment.

Statistical Analysis

Data were analyzed by descriptive statistics. The Student's *t*-test was used to assess the statistical significance of changes in best-corrected visual acuity and retinal thickness. p-value < 0.05 was considered statistically significant. All analyses were performed using the SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA).

Results

A total of 12 eyes from 11 patients (7 men) referred to our tertiary retinal center for treatment of DME. Only 1 enrolled patient was affected by bilateral CSME. The age of the patients ranged from 50 to 78 years. At baseline, mean best-corrected visual acuity (BCVA) was 0.6±0.3 logMAR. After 3 months of treatment, mean BCVA improved to 0.4 ± 0.2 logMAR. After 3 months of therapy, 0% of eyes showed reduction in visual acuity, 17% showed stabilization, and 83% showed improvement. This improvement was statistically significant ($p = 0.0072$). Average macular thickness at baseline was 358.7 ± 66.3 μm. After 3 months of therapy, 92% of eyes showed reduction of macula edema, 8% showed stabilization, and 0% showed a clinically meaningful increase (Figures 1-5). Mean macular thickness decreased to 311.1 ± 50.1 μm and the difference was statistically significant after 3 months ($p = 0.0090$). 58% of eyes showed an improvement for near best-corrected visual acuity (Jaeger) and

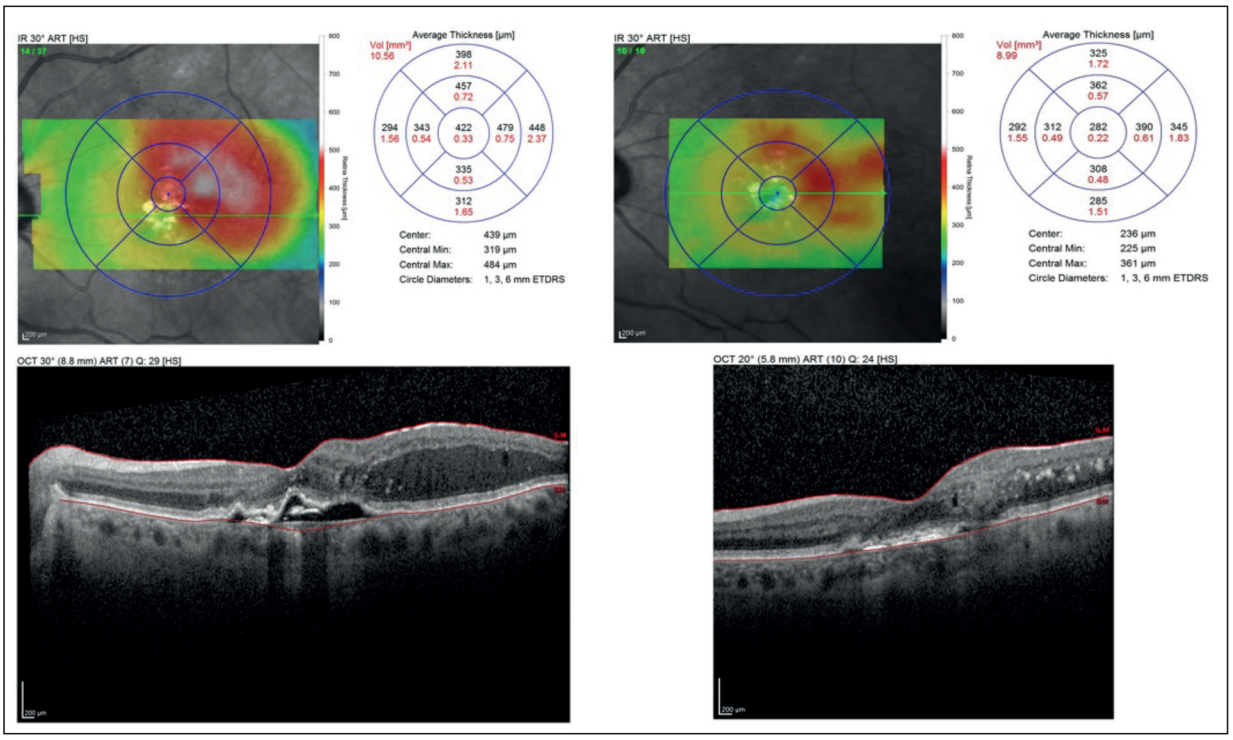

Figure 1. Retinal thickness after 3 months of treatment with Meriva®. In this case, it is possible to appreciate reduction of a subfoveal retinal pigment epithelium detachment concomitant to intraretinal diffuse edema. Subfoveal retinal pigment epithelial detachment was due to RPE dystrophy.

42% showed stability for near best-corrected visual acuity (Jaeger). No systemic adverse effects were observed.

Discussion

Anti-inflammatory agents have been used in the treatment of other exudative maculopathies[17,18], thus providing a rationale for the use of curcumin in this condition. The anti-inflammatory mechanism of curcumin is pleiotropic, and involves inhibition of proinflammatory transcription factors and enzymes at both the functional and genomic levels[7-12]. Curcumin is also an activator of PPAR-γ, a transcription factor, the stimulation and upregulation of which are associated with significant anti-inflammatory activity, with potential relevance in many ocular diseases[19,20].

Despite these interesting findings, the pharmacological potential of curcumin did not fully translate into clinical applications, given the dismally low oral bioavailability of the natural product hampering the translation of the many promising results observed in *in vitro* and animal studies into the clinical practice[21]. To overcome these issues, a lecithin solid-state dispersion of curcumin (Meriva®) has been developed, and the incorporation into a phospholipid matrix leads to an almost 30-fold increase in absorption with respect to standard formulations[14-16]. Encouraged by the activity of curcumin in inflammatory eye diseases[22-243], as well as the improvement in systemic absorption associated with Meriva®, we investigated the potential of curcumin formulated as Norflo® tablets in the management of DME. All patients completed at least 3 months of follow-up with no dropouts, indicating the excellent tolerability of the treatment and a good quality of life for patients, with follow-up visits consistently showing overall patient well-being. A relevant reversal of decreased visual acuity and improvement in the histological status of the disease (i.e., reduction of OCT retinal thickness) were observed in all patients. In view of the small number of patients in this study, its short follow-up duration, it is possible that the observed improvement was spontaneous or that resolution was simply coincident with the study treatment. Nevertheless, the reduction of macular edema, as well as improvement in visual

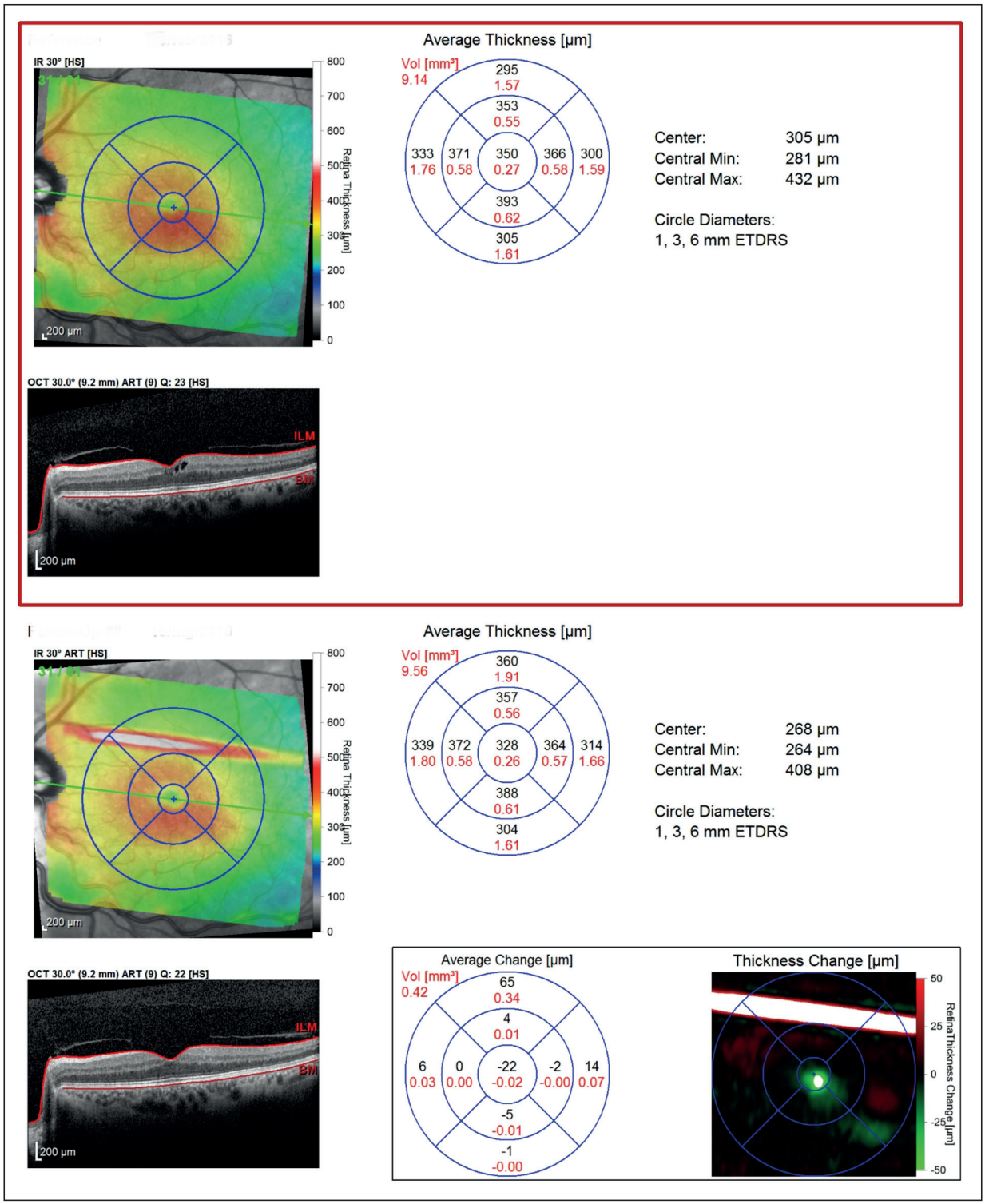

Figure 2. Reduction of intraretinal juxtafoveal cystic edema and reconstitution of the physiological foveal depression after 3 months of treatment with Meriva®.

acuity, but not necessarily disease resolution, suggests that Meriva® may be effective in the treatment of DME.

Macular edema reduction as fast as possible is considered an appropriate therapeutic aim because prolonged edema is associated with

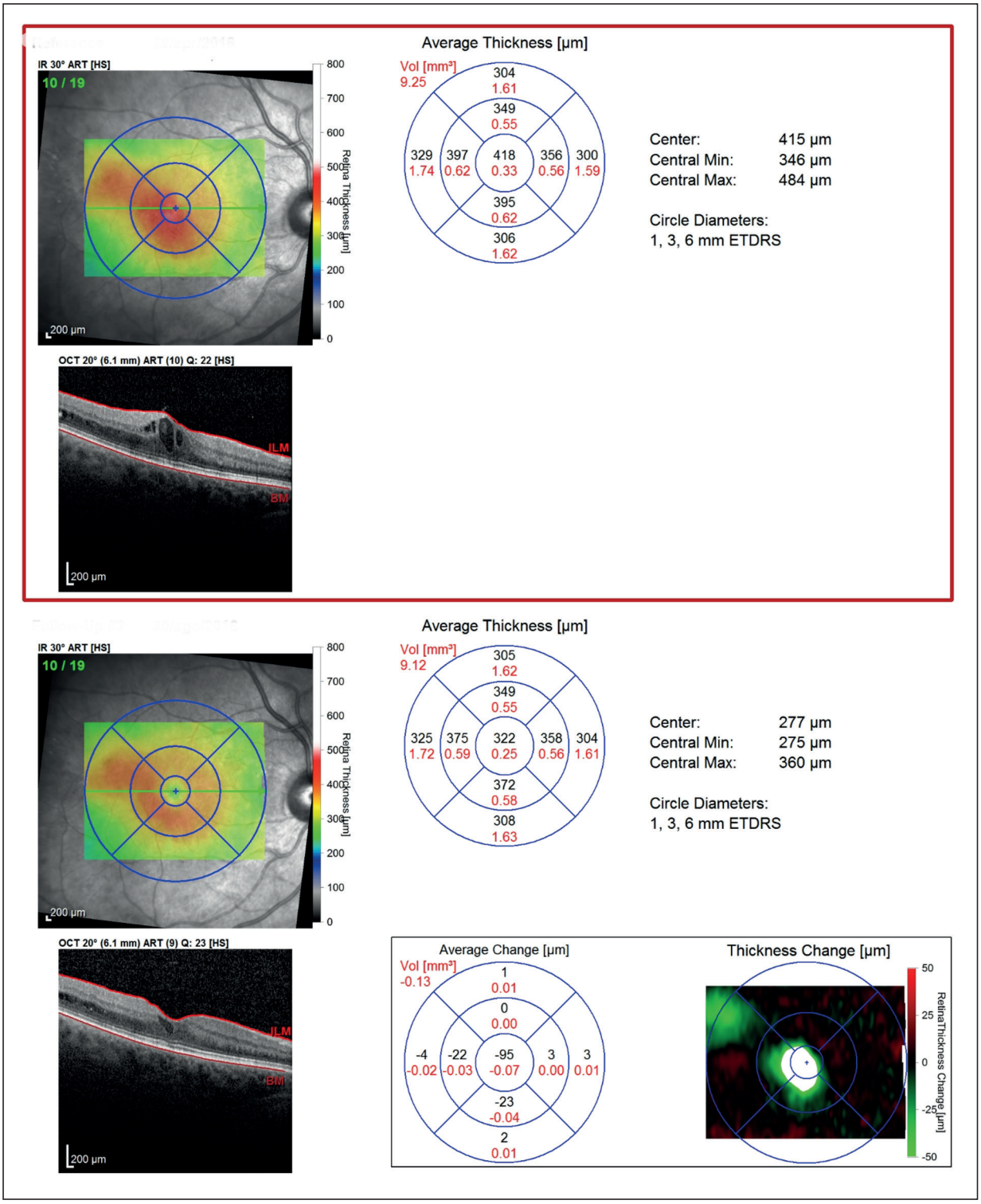

Figure 3. Reduction of intraretinal cystic edema after 3 months of treatment with Meriva®. A small intraretinal juxtafoveal cyst is still present.

atrophy of photoreceptors. Currently, there is no golden standard for the treatment of diabetic macular edema, and the treatment is resorting to controlling the underlying condition (diabetes) rather than using supportive pharmacological (anti-VEGF) or physical approaches

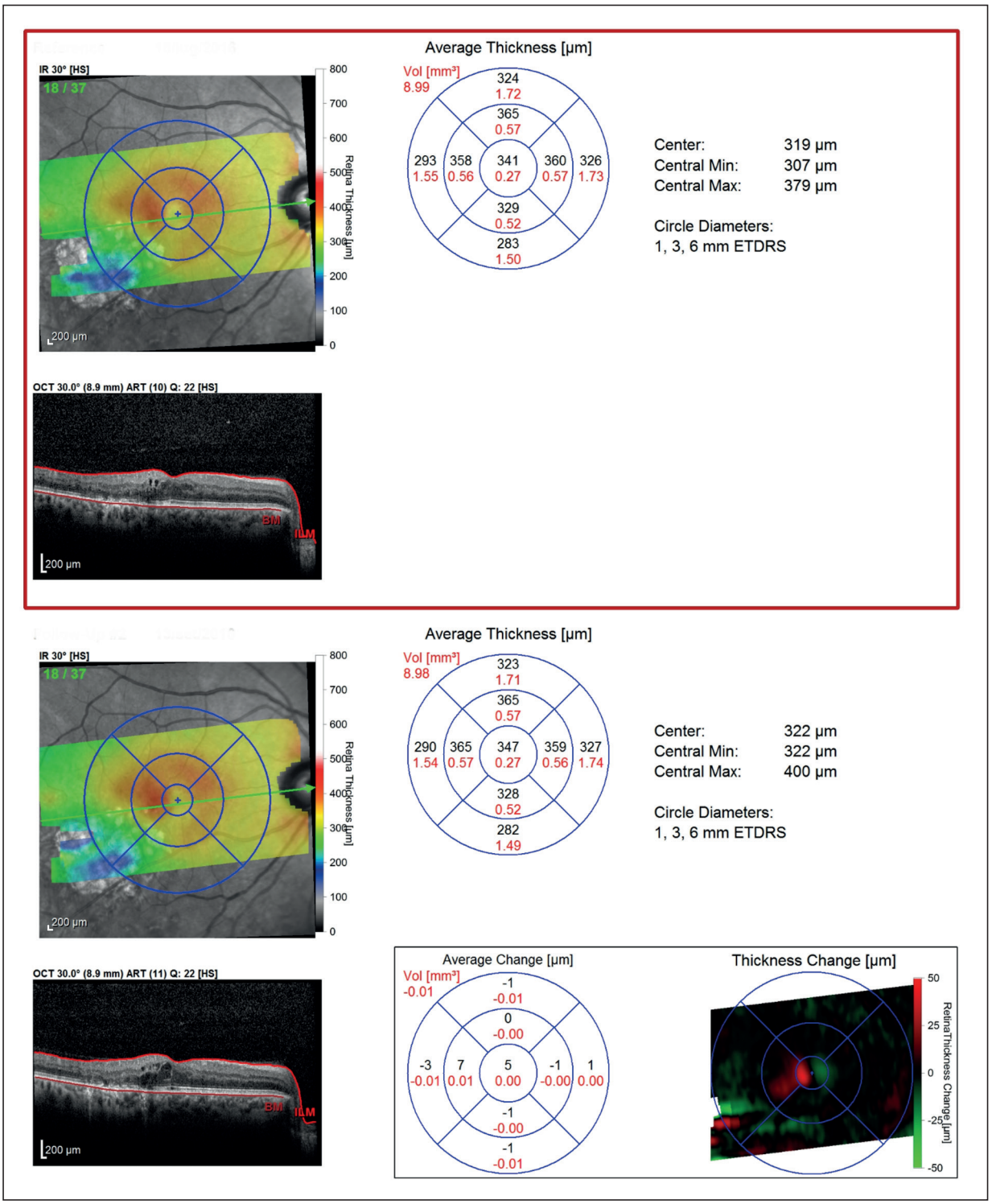

Figure 4. Stability of intraretinal juxtafoveal cystic edema after 3 months of treatment with Meriva®. The improvement in retinal thickness measured by OCT is not considered clinically significant.

(laser treatment). These considerations suggest that use of Meriva® could be helpful both as a prompt add-on therapy aimed at retinal re-attachment and as an adjunctive therapy to reduce the number of relapses in the advanced stages of the disease.

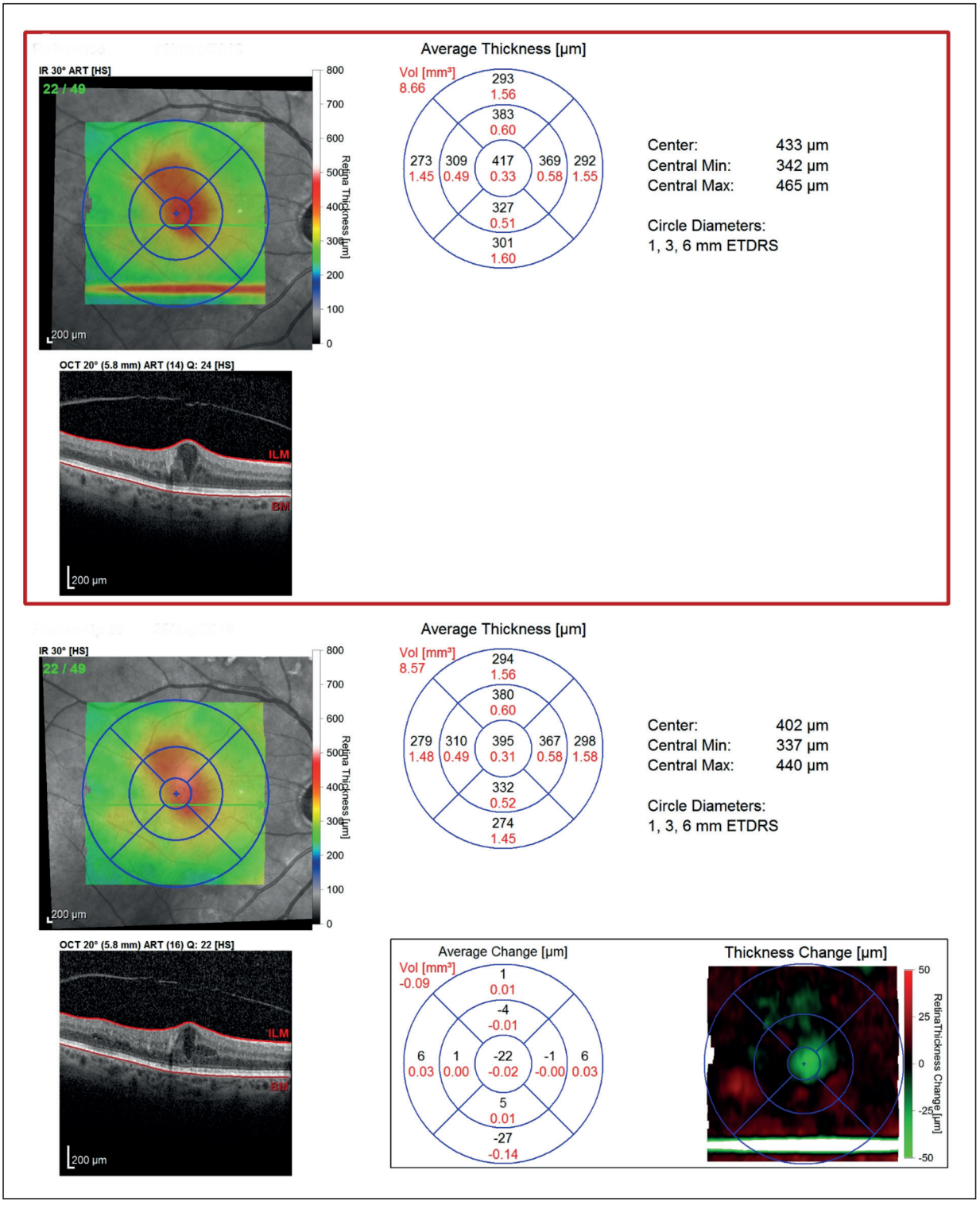

Figure 5. Reduction of intraretinal focal cystic edema after 3 months of treatment with Meriva®.

However, the inherent limitations of this pilot study in terms of number of patients, lack of a control group (although the results are similar, if not more favorable, to those reported in similar series)[1], duration of follow-up, and heterogeneity of DME should be taken into account.

Conclusions

The reported reduction in OCT macular volume, as well as improvement in visual acuity, seems very promising. We suggest that Meriva® has great potential in the management of DME, and provide a rationale for initiation of larger placebo-controlled studies that might also consider the combination of curcumin with other therapeutic options to treat this disease, such as photocoagulation therapy and intravitreal therapy.

Conflict of Interest

ST and FF are employees of Indena SpA. LG is a consultant of Indena S.p.A..

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