

Fumaric acid: a possible new therapy for macular edema?

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Received: 1 September 2017 / Accepted: 26 June 2018 / Published online: 29 June 2018
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Abstract

Introduction Causes of macular edema are multifactorial, but inflammation, vascular factors and mechanical traction are of major importance. Therapeutic options of macular edema depend on the underlying cause. Intravitreal administration of inhibitors of vascular endothelial growth factor leads to inhibition of retinal neovascularization and subsequent edema.

Objective Fumaric acid esters are successfully used in dermatology for years according to their antiangiogenic and anti-inflammatory effects.

Result For the very first time, we describe a successful therapeutic attempt for macular edema, controlled by optical coherence tomography using fumaric acid esters followed up for 60 months.

Keywords Fumaric acid ester · Macular edema · Neoangiogenesis · VEGF · HIF-1a · Transcription factor NK-kB

Case history

A then 88-year-old woman was complaining about metamorphosis and increasing visual impairment in the center of her field of vision. Testing with Amsler's net showed a central distortion. These complaints led to distinct handicap in daily life and complicated activities like reading or needlework. Regular controls by her ophthalmologist were performed.

The suspected diagnosis of a cystoid macular edema, probably in the context of age-related macular degeneration (AMD), was made, and further examinations were completed. Therapeutic options were exhaustively discussed with the patient, including repeated intravitreal injections of vascular endothelial growth factors (VEGF). The patient expressed her concerns regarding this procedure and refused to start with injections as well as to be referred to a center. Also, fluorescence angiography was not performed on patient's request.

Only few weeks later the patient presented to a dermatological routine screening, and the macular edema was mentioned by her as a recent finding. As the patient again expressed her fear of intravitreal injections, we ventured with her ophthalmologist to start oral fumaric acid esters (FAE) treatment (Fumaderm[®]; Almirall, Reinbeck/Germany). Informed consent by the patient was given before therapy started. Consent for the publication for this case report and any additional related information was taken from the patient involved in this study.

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Clinical findings

An 88-year-old female patient showed a lege artis-post-op status on both eyes as she underwent cataract surgery in 2006 and a visual acuity of 0.6/1.0. Ophthalmoscopy showed typical findings of cystoid macular edema on the right side without further changes of the anterior or posterior segments. Optical coherence tomography (OCT; Optovue, Fremont/USA) of her right eye showed distinct thickening in the center of the retina with a diameter of 440 μm (Figs. 1, 2). Neither signs of drusen nor pigment alterations could be seen. Also, no findings of vitreoretinal alteration have been observed. OCT of the left eye was unremarkable.

Diagnosis

Regarding medical history, the results of vision test, fundoscopy and OCT, the diagnosis of a clinical significant cystoid macular edema was given. Important differential diagnoses such as venous thrombosis, uveitis and Irvine–Gass syndrome were ruled out. Her history for diabetes mellitus and also her blood sugar values and HbA1c were within normal range.

Therapy and clinical course

A dose-escalating oral therapy with FAE-containing controlled-release tablets was provided, starting with 40 mg daily and increased to 480 mg daily, whereupon the patient reported repeatedly abdominal pain and diarrhea. As dosage was reduced to 240 mg daily, the patient did not complain of any gastrointestinal symptoms or flushing any more. Laboratory results

were checked regularly and stayed without pathological findings; in particular, no lymphopenia was detected at any time. However, the dose was reduced due to flushing and loss of appetite according to dose adjustment strategies well known from psoriasis patients. An individual approach is necessary to identify the specific dose of FAE for every patient regarding side effects and efficacy.

We performed clinical follow-up investigations including laboratory checkups at week two and four after initiation of the therapy with regular clinical checkups every 4 weeks. A first ophthalmological checkup was performed 4 months after the therapy was started but showed no changes of the retinal findings. At the next checkup 9 months after therapy start, cystoid changes were decreased; however, visual acuity stayed unchanged (0.6). Twelve months after start of treatment a considerable reduction in the retinal thickness; at 24 months only a mild macular edema was detected, visual acuity was 1.0 on both sides (Fig. 3), current follow-up period is 60 months. The patient continues to take 40 mg FAE daily. She is 93 $\frac{1}{2}$ years old now.

Discussion

Different causes of macular edema, like inflammation, vascular factors and mechanical traction, play an important role. Proinflammatory cytokines such as IL-6 and VEGF are being prominent players in the inflammatory process [1–3]. Also, uveitis, retinitis, vessel damage in the context of diabetes, as well as ischemia have to be considered. AMD, the leading cause for loss of eyesight in Europe in the elderly, shows macular edema [4, 5]. State-of-the-art therapy options for macular edema depend on the cause and

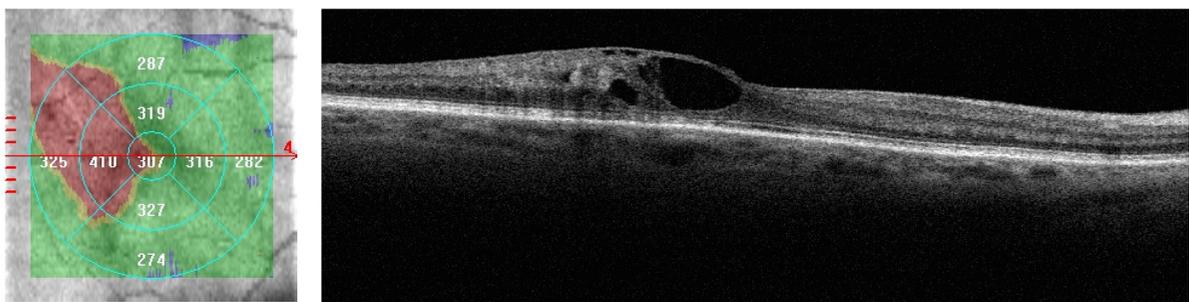


Fig. 1 OCT baseline result; distinct thickening in the center of the retina (diameter: 440 μm), cystoid changes; scanning size: 6 \times 6 mm

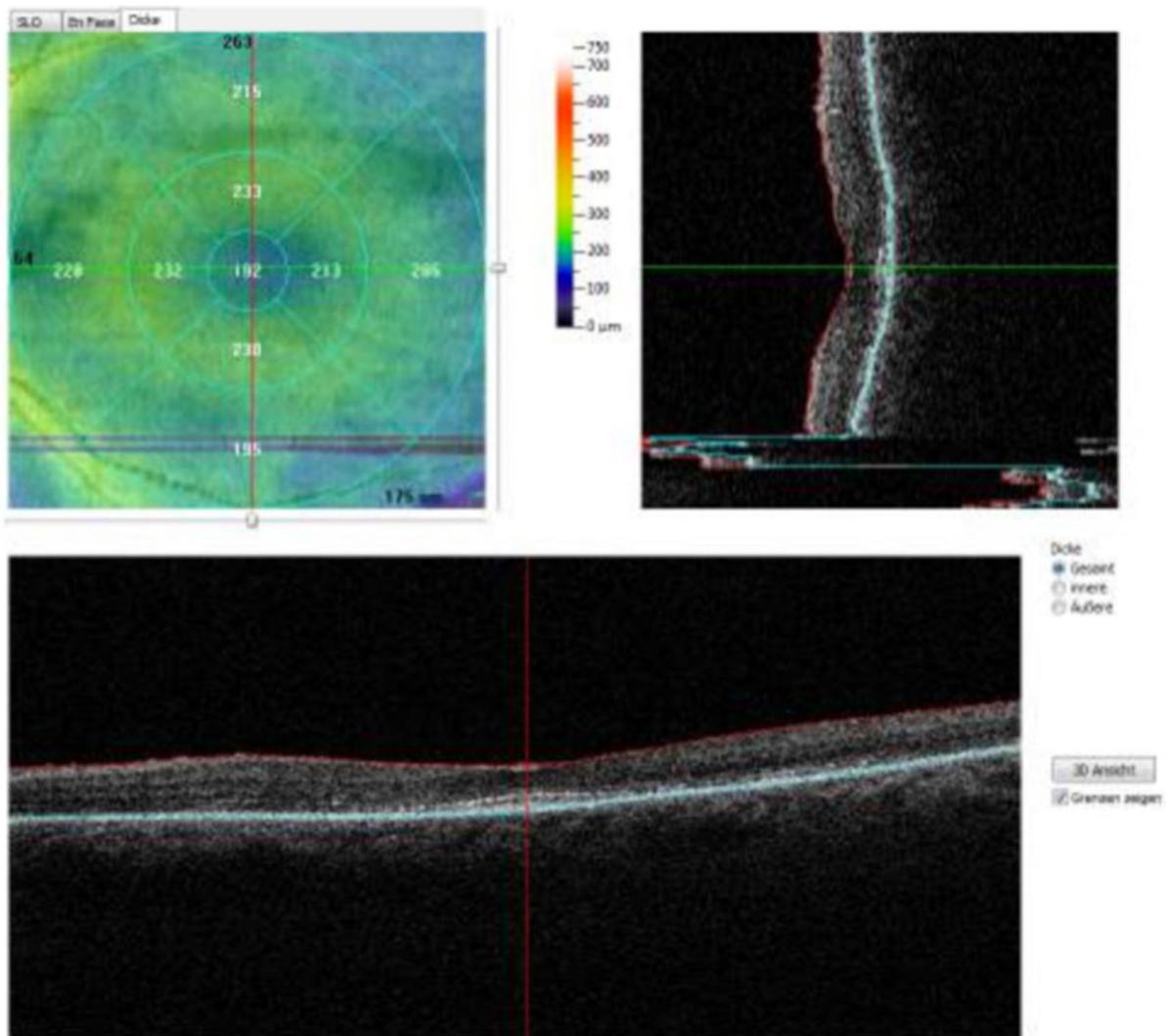


Fig. 2 OCT baseline result

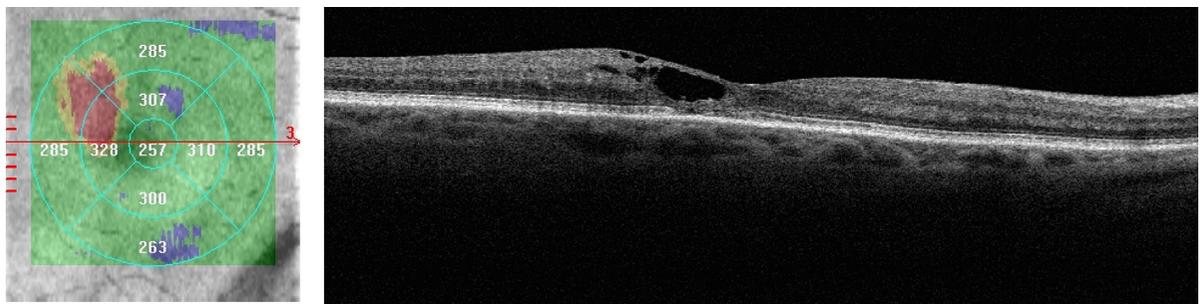


Fig. 3 OCT follow-up result after 24 month; decrease of the central retinal thickening (diameter: 337 μm) and decrease of cystoid changes; scanning size 6 \times 6 mm

include intravitreal injections of VEGF inhibitors, as well as laser coagulation [6, 7]. Especially important in the management of macular edema is the treatment of comorbidity, such as diabetes and hypertension.

FAE are widely used in dermatology for the therapy of psoriasis vulgaris. They also gained approval for the therapy of multiple sclerosis in 2013 [8–10]. The idea of using FAE instead of VEGF inhibitors resulted from their antiangiogenic and anti-inflammatory potential. Our patient receives Fumaderm[®], containing the primary component dimethyl fumarate (DMF), the methyl ester of fumaric acid; the active drug metabolite is monomethyl fumarate. FAE exert antiangiogenic as well as anti-inflammatory effects, mainly by inhibiting the proinflammatory transcription factor NF- κ B [11–15]. It seems to be likely that extracellular fumarate causes increased expression of hypoxia-inducible factor (HIF)-1 α , but downregulation of HIF-2 α . Their antiangiogenic effects are mediated by downregulation of NF- κ B and upregulation of hem oxygenase-1 [15]. It has been shown that FAE reduce cytokine levels, mainly IL-6, IL-18, IL-23 and IL-6 which might be as a possible connex in the inflammatory process in both macular edema and psoriasis [16–18]. Antiangiogenic effects of VEGF inhibitors are thus used in macular edema to inhibit growth of vessels into the retina and consequent retinal edema. As fumaric acid is a small molecule, it is reasonable to assume that it can pass easily through the blood–retinal barrier and has further effects on the retina.

After 36 months of follow-up, we first and foremost were able to demonstrate a therapeutic success verified by ophthalmoscopy, OCT, as well as vision testing. To the best of our knowledge, this is the first description of this new and maybe promising treatment of macular edema using FAE. Determining the dose of FAE is based on an individual approach, well known in psoriasis patients. Dose–effect relationship does not seem to show linear correlation.

There are weighty reasons using this therapy, in particular the possibility of oral administration, the favorable side-effect profile already known for long experience in dermatology, and also economic reasons. Moreover, FAE show only minor drug interactions, another very important point especially in elderly patients. Spontaneous remissions of macular edema have been reported, whereby in this particular case a spontaneous regression seems unlikely. The patient showed disease progression before initiation of

treatment with FAE. However, the limitation of the experience of one single patient should be noted. Therefore, no general statement about FAE in the treatment of macular edema can be made from one anecdotal report, and a discussion about its potential and further controlled studies are desirable. Our case presentation highlights good reason to believe that use of FAE will add one more option in treatment of macular edema.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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