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Treatment of ocular rosacea with 40 mg doxycycline in a slow release form

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Summary
Background: About 30–50 % of rosacea patients have ocular involvement. The symptoms range from a foreign-body sensation to conjunctivitis or blepharitis and may even include severe corneal ulcerations. Systemic treatment is generally with tetracycline. Side effects can occur with the usual antimicrobial dose.
Patients and Methods: In a retrospective study, seven patients were evaluated who had been treated for ocular rosacea with a sub-antimicrobial dose of doxycycline 40 mg in a slow-release form (Oraycea®). The responses were evaluated on the basis of clinical findings.
Results: Seven patients with an average age of 63 took slow release doxycycline 40 mg every day for at least two months. In five patients, other systemic drugs had already failed. All patients experienced a clear improvement in their ocular rosacea after an average of 2.29 months of treatment. One patient had complete clearance and another had almost complete clearance. None of the patients experienced side effects.
Conclusions: A sub-antimicrobial dose of slow release doxycycline 40 mg daily is an effective long-term therapy for ocular rosacea. It is not associated with the side effects of long-term antibiotic therapy or the risk of resistance.

Introduction
About 30–50 % of patients with rosacea have ocular involvement (rosacea ophthalmica). In about 20 % of patients, ocular rosacea is the initial manifestation of rosacea [1]. The most common symptoms of ocular rosacea are dry eyes, characterized by symptoms such as increased sensitivity to light, foreign-body sensation, redness, dryness, burning and tearing. Blepharitis is also common, and can occasionally occur with teleangiectasias which may then develop into blepharoconjunctivitis [2]. A dreaded complication is keratitis, which, if there is ulceration, can lead to blindness. There are also rare reports of iritis and scleritis. Ocular and cutaneous symptoms do not correlate with each another and ocular rosacea is thus often easily missed [1, 3]. Patients usually initially consult an ophthalmologist due to dryness of the eyes, blepharitis, or conjunctivitis. Ocular rosacea is frequently misdiagnosed as dryness of the eyes, and treatment is often merely symptomatic, consisting of administration of eye drops [2, 4]. There is currently no standard treatment for ocular rosacea. Guidelines recommend giving doxycycline 50-100 mg twice daily [1], along with proper eyelid hygiene and the use of lubricants [4]. Isotretinoin does not relieve the symptoms of ocular rosacea [5]. An interdisciplinary collaboration between dermatologists and ophthalmologists appears important.

Patients and methods
The study included 7 patients (6 men, 1 woman) with ocular rosacea who were treated on an outpatient basis with 40 mg doxycycline between 10/2009 and 12/2010. Ocular rosacea was diagnosed based on typical clinical symptoms. The average patient age was 62.57 years. Doxycycline 40 mg/daily was given in controlled-released form (Oraycea® 30 mg immediately released/10 mg delayed-release). The clinical results were evaluated as follows: 0 = no improvement, + = slight to moderate improvement, ++ = significant improvement, +++ = clearance. The average duration of treatment until initial improvement was 2.29 months and the average duration of treatment was 5.86 months.

Results
Seven patients took controlled-release doxycycline 40 mg (Oraycea®) for 2 months or longer (Table 1). Five out of seven patients had been previously treated with systemic therapies. Most patients had received higher dosages of doxycycline or were given isotretinoin. In all patients, the previous treatment

Table 1: 7 patients (6 male, 1 female) treated with controlled-release 40 mg doxycyline from 10/2009 until 12/2010.

Pat./ age m/f	**Therapy duration** months of Oraycea until first sign of improvement (total duration)	**Therapy success** (foreign-body sensation, sensitivity to light)	**Side effects** due to Oraycea	**Prior systemic therapy** (duration of therapy)	**Effects / side effects** due to prior therapies
1/50 m	3 (total 7)	++	None	Doxycycline (10 days, stopped 1 year before Oraycea)	No improvement
2/54 m	2 (total 5)	+++	None	–	–
3/58 m	1 (total 6)	++/+++	None	Doxycycline 100 mg (2 months), isotretinoin (3 months then started Oraycea)	Gastrointestinal complaints, mood disorders, headache, exacerbation of rosacea
4/85 m	3 (total 5)	++	None	Isotretinoin 10 mg (4 months, stopped 7 months before Oraycea)	No improvement
5/42 m	2 (total 2)	++	None	Doxycycline 50 mg (6 months, stopped 2 months before Oraycea)	No notable improvement, irregular use of the drug
6/84 f	3 (total 8)	++	None	–	–
7/65 m	2 (total 8)	++	None	Doxycycline 100 mg (9 months, stopped 18 months before Oraycea)	Partial improvement

regime was discontinued 2 to 18 months before treatment with doxycycline 40 mg began. The reasons were either lacking sustained improvement or side effects of treatment. In one patient, doxycycline 40 mg was given directly after ineffective treatment with isotretinoin. Another patient also failed to improve after taking isotretinoin (Figure 1a). A further patient, who had previously been given doxycycline 100 mg daily, had only partial improvement of ocular symptoms. Patient number 5 had previously been given doxycycline 50 mg daily and failed to achieve any notable improvement, though he admitted to using the drug only irregularly. Regular use of controlled-release doxycycline 40 mg led to significant improvement. Patient number 3 experienced significant side effects related to taking doxycycline 100 mg daily. Subsequent isotretinoin therapy also led to side effects. In this patient, ocular rosacea worsened during both treatment regimens (Figure 2a). All patients experienced significant improvement in ocular rosacea after an average treatment duration of 2.29 months (Figure 1b), and in one patient there was complete clearance after 5 months of treatment. Patient number 3 experienced nearly complete clearance after about 6 months of treatment (Figure 2b). There were no side effects leading to discontinuation of therapy in all patients.

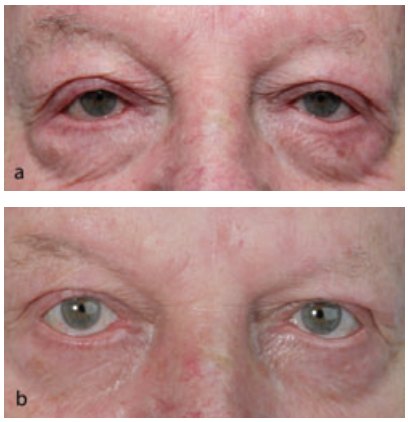

Figure 1: (a) Blepharitis 3 months before starting therapy with 40 mg doxycycline in a slow release form (patient 4). (b) Considerable improvement of symptoms 3 months after starting therapy.

Discussion

Patients with ocular rosacea usually develop blepharitis, which is characterized by blockage and subsequent inflammation of the meibomian glands, causing dry eyes (e.g., sensitivity to light, foreign-body sensation) and keratoconjunctivitis [6].

The pathophysiological mechanisms of ocular rosacea have not been fully elucidated, but the disorder is primarily an inflammatory disease in which there is increased activity of matrix metalloproteinase [7, 8]. In inflammatory eye disorders, such as ocular rosacea, instability of the tear film leads to damage of the ocular surface. The instability of the

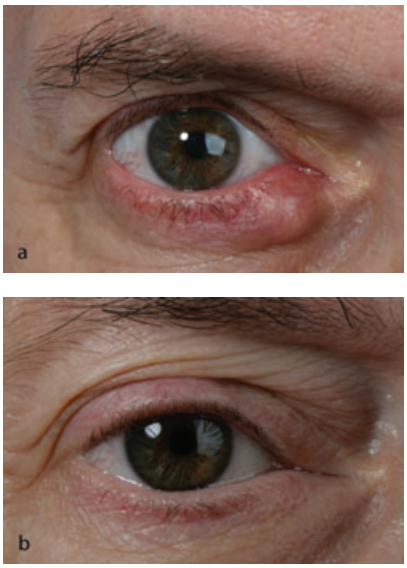

Figure 2: (a) Inflammatory nodules and blepharitis 6 months before starting therapy (patient 3). (b) Improvement of the inflammatory nodules and blepharitis 6 months after starting therapy.

tear film results in hyperosmolarity of ocular surface, stimulation of inflammatory cells, cytokine release, and activation of matrix metalloproteinase. There may also be release of endotoxins and lipopolysaccharides as well as lipase activation. This can result in eyelid inflammation and meibomian gland dysfunction which in turn can influence the stability of the tear film and evaporation lacrimal fluid, exacerbating the symptoms of dry eyes [9].

For the treatment of rosacea, mainly topical and systemic antibiotics are given such as metronidazole, erythromycin, clindamycin, and tetracyclines. The clinical effect of tetracycline in inflammatory skin disorders such as rosacea is presumably due to its non-antibiotic anti-inflammatory properties. Specifically, there is inhibition of the expression of matrix metalloproteinase, regulation of cytokines, and diminished neutrophil chemotaxis [8, 10–12].

Topical treatment of ocular rosacea includes measures to protect the ocular surface from irritation such as eyelid hygiene and the use of lubricants [4]. These measures are seldom sufficient, however. Systemic doxycycline, usually at a dosage of 100 mg daily, has been used to successfully treat ocular rosacea. Quarterman and colleagues measured treatment success with doxycycline 100 mg by tear break-up time and the Schirmer test. Clinical signs and functional tests showed marked improvement after treatment with doxycycline [3].

Yet there are drawbacks to long-term use of the drug at an antimicrobial dosage of 100 mg daily. The main disadvantages are the development of bacterial resistance and the occurrence of adverse effects which in turn may lead to lacking compliance in regard to regular use of the drug [13]. These complications make clear the usefulness of administration of doxycycline in sub-antimicrobial dosages.

Doxycycline is already highly effective when given at anti-inflammatory and thus sub-antibacterial dosages. A prospective, randomized double-blind controlled study showed the effectiveness of doxycycline given at sub-antimicrobial dosages to patients with moderate acne vulgaris [14]. In the treatment of rosacea as well, sub-antimicrobial dosages of doxycycline are highly effective while the side effect profile is more favorable and there is no antibiotic selection pressure. Gastrointestinal side effects, for instance, occur much less frequently at sub-antimicrobial dosages than at the usual dosage of 100 mg daily [15]. Such low dosages also do not involve increased sensitivity to UV light.

In the present paper we reported on 7 patients with ocular rosacea who were given controlled-release doxycycline 40 mg. There was first improvement of symptoms within a short period of time in all patients. In 2 there was complete clearance. There were no side effects.

Low-dose controlled-release doxycycline 40 mg daily may be used for effective long-term therapy of ocular rosacea without the negative side effects associated with long-term antibiotic therapy and without the risk of developing resistance. This study has shown that improvement may not be expected until after a few months. The first signs of initial improvement were seen in our study at an average of 2.29 months. We thus recommend a treatment regimen lasting a total of 6 months.

Given that ocular rosacea is a common disease, and considering that this study was performed on a relatively small number of patients, additional, larger double-blind controlled studies are needed in order to ascertain the optimal efficacy and management of the disease with long-term use of controlled-release doxycycline 40 mg. <<<

Conflict of interest
Professor Dr. Martin Schaller was a member of the advisory board in the past two years and/or received lecture fees from: Abbott, Galderma, Dermapharm, and York Pharma.

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