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

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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 telangiectasias 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 other 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 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-release 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 doxycycline from 10/2009 until 12/2010.

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

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

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 nearly complete clearance after 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.

![Figure 1a](image1a.png)  
![Figure 1b](image1b.png)
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.

References
40 mg doxycycline in ocular rosacea
